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14. ABSTRACT

This is the final report of a follow-up study of 180 subjects with Mild TBI who were treated at a Level I Trauma Center. The goal of the study was: 1) to describe the natural history of Mild TBI and 2) to identify factors that best predict long term sequelae. Most symptoms increased within 3-10 day post-injury decreased again by 3 months. Although physical symptoms had the highest prevalence, most returned to pre-injury levels by 3 months. Emotional and cognitive symptoms, however, remained elevated. Overall, approximately 36% of patients still reported four or more symptoms (defined as post-concussive syndrome, PCS), even one year after their injury. Post-injury emotional symptoms were the strongest predictors of PCS. Also, women and older patients were at higher risk of PCS. Balance problems, as assessed by balance testing, were associated with noise sensitivity, perhaps indicative of vestibular problems. In addition, while not all patients had balance testing, due to the presence of other injuries, noise sensitivity was significantly associated with subjects' inability to return to work or school at one year post-injury. The simple reaction time measure from ANAM did not predict PCS. There was no association between post-injury S100β levels and long term sequelae.

15. SUBJECT TERMS
Mild Traumatic Brain Injury (MTBI); injury; balance (BESS, Neurocom Balance Master); S-100 Beta protein ; Neuropsychological Testing (ARES ANAM); Cognitive Testing (SCATBI): Post Concussive Syndrome

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INTRODUCTION

Each year approximately 1.5 million Americans sustain a traumatic brain injury (TBI). The most common causes of TBI are due to blunt force trauma. The goal of this research was to identify a cohort of patients with mild TBI and follow them for a period of one year (1) to determine injury outcomes and (2) to identify factors that best predict patients with long-term sequelae. Subjects were recruited from the R Adams Cowley Shock Trauma Center (STC), University of Maryland Medical Center (UMMC), Baltimore, Maryland. A total of 180 subjects were recruited over the life of the study. These subjects completed a baseline assessment during the initial trauma center admission, which included biochemical markers, balance measures, clinical findings, and neurometric tests. Follow-up testing was completed at 3-5 days, 7-10 days, 3 months, 6 months, and 12 months post injury, either by return visit or telephone follow-up. This is the final report for a three-year study with an additional one year no cost extension.

BODY

METHODS:

Definitions / Inclusion Criteria:

The definition of mild traumatic brain injury (MTBI) utilized in this study is consistent both with the practice of the Shock Trauma Center and the American Congress of Rehabilitation Medicine (Ruff, et. al., 1999).

Final subject inclusion criteria were as follows:

- 18 – 64 years of age
- Blunt mechanism of injury (MOI)
- Admission Glasgow Coma Score (GCS) 13 – 15
- Presence of (at least) one of the following
    - Loss of consciousness (LOC) <30 minutes
    - Loss of memory of events immediately before or after the injury
    - Alteration of mental state following the injury such as confusion, disorientation and feeling dazed
- Acceptable score on the Mini Mental State Examination (8/10 on orientation)
- English speaking

Additional exclusion criteria included:

- Presence of complicating factor
    - Brain lesion on CT scan requiring clinical intervention
    - Moderate/severe multiple trauma
    - Focal neurological findings
    - Skull fracture requiring clinical intervention
    - Cerebrospinal fluid (CSF) leak requiring clinical intervention
    - Prior brain injury (moderate or severe)
    - Posttraumatic amnesia exceeding 24 hours
    - Seizures (new or prior history)
- History of psychiatric disorder requiring hospitalization or a history of hallucinations
- Recent pre-injury history of substance abuse
- Current probation or parole
- Active duty military

Human Subjects Protections / Protocol Modifications:

The University of Maryland Baltimore (UMB), Human Research Protections Office (HRPO) and the Human Subjects Research Review Board (HSRRB) at the Department of the Army approved the study protocol in July 2003. A HIPAA waiver of authorization was received from UMB to allow screening for study recruitment. A Certificate of Confidentiality for the study was received from the Department of Health and Human Services in March 2003, and extended in August 2006 through March 2008.

Annual protocol renewals have been completed during the life of the study. The UMB-HRPO Institutional Review Board (IRB) recently provided re-approval for the protocol for a one-year period beginning March 29, 2007. Continuing Review was submitted to the HSRRB on April 10, 2007.

Protocol amendments were made in November 2003, January 2004 and June 2004 to expand eligibility criteria to enhance subject recruitment. Other protocol amendments were made due to changes in personnel.

Test Development / Schedules:

Finalization of the testing instruments scheduling of administration and IRB approvals were completed during the first 6 months of year 1. Several initially proposed tools were not in the final implementation. The Modified Galveston Orientation and Amnesia Test was replaced with the original Galveston Orientation and Amnesia Test (GOAT), as the modified version had not yet been reported in the literature. The Symptom Checklist was changed to a version providing more objective documentation of post-concussive symptoms including intensity and frequency of symptoms. The Computer Assessment of Response Bias (CARB) was removed due to proprietary issues.

Sequencing of test administration also required modification during the first 6 months of year 1. The entire battery required between 2 ½ and 3 hours to administer. Determining the best sequence to achieve maximum subject participation required numerous trial sessions with study staff serving as test subjects. Ultimately, while a desired sequence of evaluation components was identified, subject tolerance and availability (especially during the initial assessment) of subject and staff dictated the actual sequence. Ideal sequencing would have the interview and all cognitive components performed prior to balance testing. Frequently, however, subjects expressed a need for a break during the cognitive testing (which can take up to 2 hours by the 3 month assessment), and performance of balance testing at the mid-point aids in effective completion of the entire test battery. The actual sequence of test components was recorded for each session in case of the need for future data analysis of the impact of sequencing on results. Table 1 details the assessment components for each evaluation period.

Table 1: Evaluation Components

Initial Assessment	3-5 Days Post-Injury	7-10 Days Post-Injury	3 Months Post-Injury	6 & 12 Months Post-Injury
Screening				
Consent				
S-100 Processing				
Initial Interview	Interview	Interview	Interview	Interview
Symptom Checklist	Symptom Checklist	Symptom Checklist	Symptom Checklist	Symptom Checklist
Well-Being Scale		Well-Being Scale	Well-Being Scale	Well-Being Scale
ARES	ARES	ARES		
GOAT				
SCATBI		SCATBI	SCATBI	
		WMT (immediate)	WMT (immediate)	WMT (immediate)
		ANAM	ANAM	ANAM
		WMT (delayed)	WMT (delayed)	WMT (delayed)
BESS	BESS	BESS	BESS	BESS
Balance Master	Balance Master	Balance Master	Balance Master	Balance Master

See definitions below

Overview of Evaluation Components and Methods

Screening and Consent:

Designated research staff completed daily review of the STC new admission listing for potential study subjects. Subjects meeting inclusion criteria were approached during their hospitalization at STC within 3 days of their injury and eligibility for the study was confirmed via questioning. Standard consent procedures were followed with all potential subjects including administration of the Mini-Mental Status (MMS) examination. Subjects achieving at least an 8/10 were asked to consent to the study and sign both the standard consent form and HIPAA authorization form. Subjects who did not achieve an 8/10 on the MMS were not consented at the time of initial contact. A return approach was made later in the subject's hospital stay and if the MMS score was then acceptable, consent was pursued. Subjects who were unable to sign the consent and HIPAA authorization forms, were able to give witnessed verbal consent. When possible the witness was a member of the medical staff (most often bedside nurse). Once consented, each subject received a Subject Information Packet that included copies of consent and HIPAA authorization forms, welcome letter with study contact information, Mild TBI information packet, and directions and maps for follow-up appointments.

Biochemical Markers - S-100β testing:

After consent was obtained, research staff contacted the STC clinical lab for retrieval of blood samples. The blood utilized for the S-100β testing was the remainder of a prior blood draw, usually one performed on admission to STC. Approximately 5 ml of serum was collected, spun down and frozen at -20° C. The frozen samples were then collected by the UMB Clinical Chemistry Lab staff and processed in batches of 30 samples. A procedure to ensure timely retrieval and freezing of blood samples per testing guidelines and moving of the samples to the

research lab for storage until ready for bulk processing was established. Processing was completed as described in the Nexus Dx 2-100 Test Kit, SynX Pharma Inc.

Initial Interview and Assessments:

Initial interviews were administered following consent during hospitalization. Research interviewing staff worked in conjunction with the Speech Language Pathologists to complete the initial evaluation. When possible all initial components were completed in succession. Occasionally, cognitive or balance components would be deferred until later in the day or the following day due to subject tolerance or other medical care issues. When subjects were unable to continue or deferred completion of all components of the initial evaluation, priority was given to the intake interview, symptom checklist, and ARES(ANAM {Automated Neuropsychological Assessment Metrics} Readiness Evaluation System). This assessment included:

- Intake Interview containing Demographic characteristics, Medications – prior to injury and since admission, Past medical history including prior TBI, CAGE and Drug CAGE questions to identify subjects with possible substance abuse disorders (Ewing, 1984)
- Symptom Checklist containing 12 symptoms encountered after TBI. Subjects initially were questioned regarding the presence, frequency and intensity of each symptom in the week prior to the injury (Miller, 1998)
- The Psychological General Well Being Scale, an index measuring a person's subjective well-being including 22 questions within the six domains of Anxiety, Depressed mood, Sense of positive well-being, Self-control, Vitality, and General health (McDowell, 1996)
- The ARES is discussed further under neuropsychological testing (Elsmore, 2007)
- The GOAT (Galveston Orientation and Amnesia Test) is discussed further under cognitive testing (Levin, 1979)
- The SCATBI (Scales of Cognitive Ability for Traumatic Brain Injury) is discussed further under cognitive testing (Adamovich, 1992)
- The BESS (Balance Error Scoring System) and Balance Master protocols are discussed further under balance testing (Riemann and Guskiewicz,2000)

***The Concussion Symptom Checklist*:**

The checklist consists of answers to questions regarding twelve concussion-related symptoms, including questions related to 6 physical, 3 emotional, and 3 cognitive domains. Each question addresses symptoms experienced during the past week, including the number of days involved and the severity of the symptom, on a scale from 1-10.

Neuropsychological Testing:

The ANAM, ARES, and Word Memory Test (WMT) constitute the neuropsychological battery of tests that are designed to measure cognitive, emotional, and motivational functioning.

The ANAM is a Performance Assessment Battery originally developed in conjunction with the US Army as part of the Walter Reed Performance Assessment Battery. The battery of tests

selected for use in this study included 9 subtests that required between 35 and 45 minutes completing. Subtests chosen included tests of simple and choice reaction time, divided attention of visual and spatial skills, running memory and executive reasoning. Subtest content does change with each subsequent exposure to the test, unless the subtest was not "passed" at the previous exposure. The ANAM battery was completed on a laptop with an external mouse. The ARES, a palm pilot version of selected ANAM subtests, was also utilized. This version contained 3 subtests including sleep scale, simple reaction time and continuous performance test. The ARES required approximately 10 minutes to complete.

Subjects were first exposed to the ARES as part of the Initial Assessment. Orientation to the use of a palm pilot was performed for all subjects, including use of the palm buttons; the stylus was not used for any of the ARES testing. Modifications to allow single hand use for those subjects with hand or upper extremity injuries were made. If subjects reported inability to see the palm screen due to eye injuries or lack of eyeglasses/contacts, a second attempt to complete ARES testing was offered on the same day. If the subject was still unable to complete testing no further attempts were offered for that evaluation timeframe. ARES testing was completed at the Initial Assessment, 3-5 Day, and 7-10 Day follow-ups, when possible.

Initial ANAM exposure occurred at the 7-10 Day follow-up as it was felt that most subjects would be able to tolerate the 35-45 minutes required to complete the testing by then. ANAM testing was completed at all subsequent follow-ups throughout the study. Subject orientation to a laptop computer and mouse was performed prior to testing, and subject handedness recorded. In the case of dominant hand or upper extremity injury the use of the non-dominant hand on initial contact was recorded and held consistent through all subsequent testing, regardless of recovery of the dominant hand. All ANAM components were attempted on at least the first exposure. If a subject expressed strong frustration or requested termination of a particular subtest, the identified test was skipped, but the remainder of the battery was attempted. For a small number of subjects who expressed poor reading and math skills prior to injury, particular subtests were omitted after the first attempt.

The WMT, a brief paper and pencil test, measures sensitivity to motivation and embellishment of cognitive deficits, i.e. 'malingering'. During this test the subject is read a list of 40 paired words twice. Following presentation of the target stimuli, the subject is tested for immediate word recall and for delayed recall (30 minutes later). Following the delayed recall trial, a multiple choice test is administered, where the subject is given the target word and then must choose the correct paired word, as presented during initial presentation of the words. The word lists do not change from exposure to exposure. First exposure to the WMT occurred at the 7-10 Day evaluation and continued through all subsequent follow-ups.

Cognitive Testing:

The GOAT (Levin, 1979) is utilized in the acute care setting to determine the length of a subject's post-traumatic amnesia. Speech Language Pathologists (SLP) routinely administer this tool during their initial assessment, and for purposes of the study the interview staff were also trained to administer the test. Questions include general orientation to person, place and time as well as memories both prior to and immediately after the injury. The GOAT was administered only once to each subject either, by the interview staff at initial intake or by the SLP staff prior to SCATBI testing.

The SCATBI, which is also administered by the SLP staff, provides a systematic method of assessing cognitive deficits following TBI for patients with injuries ranging from mild to severe, and consists of five different scales designed to measure aspects of cognitive/linguistic performance. Subtests are organized in broad categories of perception and discrimination, orientation, organization, recall and reasoning. Each category contains several "testlets" of increasing difficulty. For purposes of this study, the perception and discrimination section was omitted as these testlets demonstrate lower level functioning. Testlet content does not change from first subject exposure to subsequent exposures. The time required to administer the SCATBI for this study ranged from 35 to 50 minutes. First exposure with the SCATBI occurred during the initial assessment, and subsequently at 7-10 Day and 3 Month follow-ups. The decision to not continue SCATBI assessment after the 3 month timeframe was made due to the time consuming nature of the test and based on discussion with SLP staff who reported infrequent experience with clinical use of the SCATBI beyond 3 months post-injury.

Balance Testing:

Two components were utilized for this study to assess balance, the Neurocom Balance Master (NBM) and the Balance Error Scoring System (BESS). Good inter-tester and intra-tester reliability and validity compared to the NBM has been established for the BESS.
Prior to balance testing at the initial assessment, clearance from the medical team was obtained. For subsequent assessments, balance was only evaluated if the subject was cleared for full-weight bearing without activity restrictions on both lower extremities. Subjects were also excluded from balance testing due to other associated injuries, or on-going medical evaluation or conditions (i.e. pregnancy). Table 2 highlights the reasons balance testing was not completed at initial assessment.

Table 2: Balance Testing – Reasons Not Completed at Initial Assessment

Reason Not Tested (may have 1 or more reasons)		**Frequency**
Lower Extremity Fracture/Injury		
	Pelvis	30
	Femur	13
	Patella	1
	Tibia/Fibula	16
	Foot	6
Upper Extremity Fracture/Injury		29
Chest or Abdominal Injury		58
Spine (boney) Injury		30
Facial Injury		13
Skull Fracture/Head CT Findings		7
Symptoms (i.e. dizziness, nausea, vomiting)		10
Past Medical History		6

The NBM is a computerized medical device that includes a SMART EquiTest ™ system for evaluating standing balance in a variety of situations (normal vision, absent vision, sway referenced vision, fixed support, mobile support) and is standardized for age. Reliability, sensitivity, and validity are established for the NBM system and it has been found to be a useful predictor of the length of rehabilitation and psychosocial and vocational outcomes. A significant drawback of its use in field tests for balance and outcome following TBI is that the NBM is a large piece of equipment that cannot be easily moved from a controlled situation.

The test protocol consists of 18 trials (20 seconds each), in which the subject is asked to stand as motionless as possible with the feet shoulder-width apart on a force platform. A composite equilibrium score describing the subject's overall level of performance during all trials is calculated. First encounter with the NBM occurred at initial assessment, when possible, and at all subsequent follow-up assessments.

The BESS requires very little equipment (stopwatch, 46 X 46 X 13 cm medium density foam surface) and can be used in a variety of settings as a clinical field test of postural stability and balance. In this test, vision is eliminated while balance is assessed during bilateral, unilateral, and tandem stance first on a firm surface and then on foam (20 second trials of each). Error points are scored based on the number of times a subject moves out of the test position or opens his eyes during each 20 second trial. BESS testing was conducted at the initial assessment and follow-up assessments, whenever possible.

Well Being Scale:

The General Well-Being Schedule (GWB) is a brief indicator of subjective feelings of psychological well-being and distress. The scale, which was administered by the clinical coordinators, is a self-administered questionnaire that was developed for the U.S. Health and Nutrition Examination Survey (HANES I), assesses how the individual feels about his "inner personal state", rather than about external conditions such as income, work, environment, or

neighborhood. It reflects both positive and negative feelings: six dimensions cover anxiety, depression, general health, positive well-being, self-control, and vitality.

The GWB includes both positive and negative questions. Each item has the time frame "during the last month." Therefore, for the initial screening visit, the answers to the Well-being questions refer to the one month period pre-injury. However, for the 7-10 day visit, the subject was instructed to answer the questions for the period since their injury, and not the past month; for all other visits, the 30-day time frame was maintained.

Follow-up Assessments:

Follow-up assessment components and timeframes are described in Table 1. Attempts were made to have subjects return for complete assessments whenever possible for each timeframe. For those subjects who were unable to return for on-site assessment, an abbreviated phone interview was completed in order to ascertain current symptoms experienced by the participants. A detailed procedure for follow-up contact and scheduling of appointments was developed. Study participants who completed follow-up assessments either by on-site visit or phone received nominal compensation for their participation, as described in the study consent and in Table 3 below.

Table 3: Subject Compensation

	3-5 Day	7-10 Day	3 Month	6 Month	12 Month
Interview and designated components	$50	$75	$50	$75	$100
Telephone follow-up	$10	$10	$10	$10	$10

Administrative Components:
Staffing / Training:

Since the beginning of the project staff members have been consistently oriented and trained by existing staff members and the Study and Clinical Coordinators. A copy of selected policies and procedures was provided upon orientation to all new clinical staff members. Periodic assessments were performed to ensure inter-rater reliability of the formalized components of the evaluations (balance, speech and neuropsychological testing). As described in previous reports, during the life of the study multiple staff members from both Neuropsychology and Speech Language Pathology provided increased hours of coverage and flexibility in staffing in order to complete the maximum number of initial and follow-up evaluations. Ultimately, clinical staff support was utilized from the Baltimore Veterans Hospital Neuropsychology Department and the University of Maryland Medical Center Rehabilitation Services Department (speech and initial physical therapy staff).

A complete listing of all research staff during the life of the study is found in Appendix B. All members of the research staff completed the Certified Investigator Training Initiative (CITI) annually as required by UMB HRPO. Appendix B also identifies those staff members who will have a continued role in data analysis and dissemination through March 2008.

Manual of Operations:

An extensive manual of operations was created prior to the initiation of subject recruitment to ensure consistency and clarity for the numerous staff members working on and with the study. Policy and procedures were developed to cover the recruitment and follow-up scheduling of subjects, individual evaluation component procedures and reporting, and administrative tools including data entry, verification, migration, and back-up. Subject specific policies included: subject consent and authorization, overview information, storage and organization of subject files, safety procedures, adverse event reporting, and subject compensation for participation. All policies and procedures were reviewed by the appropriate team members and matched to institutional and governmental regulations for consistency when appropriate. Master binders were kept in both the central study office and the satellite testing area for easy reference, and updates were made as necessary throughout the life of the study.

Resource manuals containing relevant research articles, manufacturer instructions, and keys for test interpretation were also created and available for staff use.

Safety:

Since this research endeavor involved direct contact with subjects both as in-patients at the STC and upon return for follow-up evaluations, numerous safety procedures were established and maintained. A decision tree was created to aid in the appropriate notification of medical staff in the event of an adverse response to testing procedures. Policy and procedures for handling patient care issues or code situations were defined. Safety equipment, including gait belts/harness system for balance testing, blood pressure cuff, stethoscope, and portable oxygen tank were maintained in the STC office. Notification of the hospital code team was completed and location of the nearest hospital crash cart was posted along with emergency procedures in the STC office. Safety measures included the addition of two telephone lines into the testing office to allow for paging of staff in the event of an emergency. Safety for research staff members as well as subjects was also considered, and the need for two study staff was frequently warranted. A second staff member was present during all balance testing, most initial evaluations, and during follow-up evaluations when there were multiple post-concussive symptoms reported or when subjects demonstrated personal space boundary issues. A procedure was also developed in the event that a subject articulated or demonstrated behaviors that indicated a need for psychiatric counseling. Annual Biomedical Engineering checks were also required for the NBM.

Space Allocation:

During the life of the study two different office areas were utilized for follow-up testing. Both areas needed to be large enough to house the NBM, provide adequate floor space for the BESS balance testing and sufficient desk area for completion of the computerized neuropsychological tests and interview components and comfortably allow 3 people to occupy the space simultaneously if needed. Initially, space was allocated on the first floor of the hospital, next to the STC follow-up clinic which was extremely convenient for our subjects. During year 2, due

to space allocation within STC, the study office was moved to a lower level in the hospital. During the move, the NBM was unavailable for several days in order to have the manufacturer assist in the relocation and the recalibration of the system.

Team Meetings:

Meetings of the study team occurred on a regular basis. During the first year of the project, meetings occurred on a bi-weekly to monthly basis. Throughout the remainder of the active recruitment and follow-up phase, meetings were held bi-monthly or as needed. These meetings focused primarily on issues related to recruitment, follow-up and participant recovery. Additional small group meetings were held as needed focusing on specifics such as data entry and preliminary analysis for the various components of the study. The frequency of small group meetings has now increased to bi-weekly as the data analysis phase has progressed.

Data Entry and Storage:

Access data base forms and a data back-up process were developed for each of the evaluation components delivered via paper and pencil prior to the start of subject recruitment. Data back-up and migration procedures to an Access database were developed for the ARES and ANAM computer-based tools. Downloading of the NBM computerized data and electronic migration proved challenging due to software interface issues, and a manual data entry system for the key data elements was developed during year 2 of the project.

Training of research staff was completed for data entry and auditing. Data were routinely entered into the Access database within 48 hours of evaluation completion and data migrations from the computerized systems were completed on a weekly basis. One clinical coordinator and the part-time recruiter were responsible for all data entry and the second clinical coordinator was responsible for auditing all data. In addition, prior to analysis a secondary data validation was completed and changes to the data were recorded.

ANAM Proprietary Issues:

All study staff administering the ANAM or ARES were required to sign software usage agreements, as the software is the proprietary information of the USAMRMC. Software usage as well as data collection, storage and analysis were consistent with the user agreement throughout the life of the study. In order to utilize these test batteries, 2 laptops and 5 palm pilots were procured for exclusive use with these tests.

Data Analyses:

The initial phase of the analysis focuses on describing the screening, recruitment and follow-up periods of the project in terms of potential and recruited subjects. A description of the final

population of recruited blunt trauma victims is made in terms of demographic information (e.g., age, gender, pre-injury employment, marital status, education), injury characteristics (e.g., mechanism of injury, admission Glasgow Coma Scale [GCS] scores, Injury Severity Score [ISS]) and medical history (e.g., previous brain injury, pre-injury depression status, pre-injury substance use as measured by the CAGE). The natural history of post-concussive symptoms during follow-up, as assessed by the 12-item Mild TBI Symptom Checklist and grouped in terms of physical, cognitive and emotional domains, is analyzed in tabular and graphic form to describe the change in prevalence of specific symptoms over time. Additional analysis compares the natural history between the two cohorts of subjects who (a) experienced a specific symptom between 3 and 10 days post-injury and (b) did not experience a specific symptom between 3 and 10 days following injury. These data are presented to demonstrate if subjects suffering particular symptoms immediately following injury were more likely to sustain persistent, long-term symptomatology than were study participants who did not report the same post-injury symptom during the 3 to 10 day follow-up period.

Contingency table analyses (e.g., Pearson's chi-square and Fisher's exact test), the Student's *t* test, analysis of variance (ANOVA) and correlation coefficients are used to determine associations between the above baseline variables and specific covariates of interest, such as scores generated by: (1) the S-100β blood test; (2) the ANAM; (3) the ARES; (4) the SCATBI; (5) the symptom checklist; and (6) the Well-Being Rating Scale. The rationale for this part of the analysis is to investigate the degree of correlation between independent variables and to allow for the removal of redundant information that might otherwise provide misleading results. As this portion of the analysis plan is largely exploratory in nature, a probability value of 0.05 is used to indicate statistical significance.

Variable clustering correlation methods were applied to determine the best way to group individual symptoms as listed on the symptom checklist for data analysis. Results of the procedure indicated that symptoms could be grouped into 3 domains: physical, cognitive and emotional. Additional clustering analysis indicated that the total well being score ascertained from the Well-Being Rating scale was a more appropriate use of this instrument.

Receiver operating characteristic (ROC) curves are also constructed to examine the sensitivity and specificity of initial S-100β serum concentrations among specific groups of subjects and with respect to various outcome measures, including follow-up reporting of 4 or more symptoms using the symptom checklist. Due to the non-normal nature of S-100β data, Wilcoxon rank-sum statistics were used to determine if S-100β levels were elevated for specific types of injury other than that to the head (i.e., upper extremity, thoracic, abdominal, and lower extremity).

During the second phase of the analysis, individual linear regression models are conducted to determine variables that are predictive of the following outcome measures assessed on a continuum at 3 months, 6 months and 12 months: (1) the number of symptoms, as reported using the symptom checklist; (2) the severity of reported symptoms, and (3) the lack of well-being, as reported using the Well-Being Rating Scale. Symptom severity was calculated by an algorithm incorporating the intensity of the particular symptom on a scale of 1 (low) to 10 (high) and its persistence over time in terms of number of days. A plot of the severity scores indicated a non-normal distribution for various baseline measurements; hence symptom severity was

transformed using the natural logarithm to provide an outcome measure that was approximately normal. Initial regression models independently examined demographic, injury and medical measurements assessed at baseline, in addition to various post-concussive symptoms reported between 3 and 10 days post-injury, as potential univariate risk factors for outcome before inclusion of all relevant variables in a multivariate model. If sample sizes permitted, factors representing the ANAM, SCATBI, and balance measures (i.e., the Sensory Organization Test {SOT} composite score and the BESS score) were then entered as covariates to ascertain whether associations between outcome and measurements taken during the early testing sessions are improved when neuropsychological, speech and balance information is added to each model. Univariate main effect analyses indicated that the simple reaction time thruput score (SRT) as measured by ANAM and the recall feature of the SCATBI were highly associated with outcome; thus, these two factors were included in subsequent models as surrogates for the ANAM and SCATBI, respectively. Special emphasis will be placed on models describing predictors of outcome measures that are collected at the point in time, whether it be at 3 months, 6 months or 12 months, when recovery seems apparent.

Finally, multivariate logistic regression models are constructed to evaluate possible predictors for dichotomous outcome measures at 3 months, 6 months, and 12 months, including (1) the reporting of 4 or more symptoms using the symptom checklist and (2) the inability to return to work or to pre-injury student activity. Independent variables include demographic, injury and medical measurements assessed at baseline, in addition to various post-concussive symptoms reported between 3 and 10 days post-injury and baseline measurements of the SOT, SRT and SCATBI recall information. For these regression models, continuous data such as age and S-100β are expressed as design variables in terms of tertiles because of the possibility of the logit, as a function of such variables, having a non-linear shape.

LITERATURE REVIEW:

Background:

Magnitude of the Problem of Traumatic Brain Injury (TBI):

The Centers for Disease Control (CDC) has estimated that each year approximately 1.5 million Americans sustain a TBI, of whom approximately 230,000 are hospitalized (Thurman et al., 1999). In addition, approximately 50,000 Americans die each year following TBI; this figure represents one-third of all injury-related deaths. The most common causes are motor vehicle crashes, falls, and violence, with an increased incidence of bicycle and sports-related injuries among the young. Adolescents, young adults, and the elderly are at the highest risk of incurring a TBI. From 1980-1994, the TBI-associated death rate in the United States decreased 20% from 24.7 per 100,000 population to 19.8 per 100,000 population. Most of the decrease resulted from a decline in transportation-related deaths, although rates of TBI-related deaths due to falls and other causes also decreased during this period. However, during this same period, firearm-related TBI deaths increased 11%; as a result, firearm use surpassed transportation crashes as the leading cause of TBI in 1990. The highest rates were noted among those aged 75 years and older, with a smaller peak among those aged 15-24 years.

Based on one study, the annual economic burden of TBI in the United States was estimated to be approximately $37.8 billion in 1985 (Max et al, 1991). However, this study did not account for the intangible costs borne by families of those who die prematurely from head injury, or for the physical and emotional costs attributable to lifelong disability following TBI.

It has been estimated that approximately 80-85% of TBI that occur each year in the United States are considered mild. However, most epidemiologic studies have primarily addressed more severe head injury fatalities or injuries resulting in hospitalization. Rates of TBI hospitalization have declined significantly during the past 20 years, in part due to successes in injury prevention and also to changes in hospital admission practices that shift the care of persons with less severe TBI from inpatient to outpatient settings. The National Center for Health Statistics (NCHS) National Health Interview Survey has provided some information on the incidence of TBI treated on an outpatient basis. In 1991, an estimated 1.54 million non-institutionalized U.S. civilians sustained brain injuries that resulted in LOC but were not severe enough to cause death or long-term institutionalization (Sosin et al., 1996). Of this group, 25% received no medical care for TBI, 49% received care in an emergency department (ED) or other outpatient site, 9% received overnight hospital care, and 16% were admitted to a hospital for two or more days.

Mild TBI:

The American Congress of Rehabilitation Medicine (Ruff et al., 1999) defines mild traumatic brain injury (MTBI) as a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: any period of LOC; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g. feeling dazed, disoriented, or confused); and focal neurological deficits that may or may not be transient, but where the severity of the injury does not exceed the following: posttraumatic amnesia (PTA) not greater than 24 hours; after 30 minutes, an initial Glasgow Coma Scale (GCS) score of 13-15; and LOC of approximately 30 minutes or less.

This definition includes: 1) the head being struck, 2) the head striking an object, and 3) the brain undergoing an acceleration/deceleration movement (i.e., whiplash) without direct external trauma to the head. Computed tomography (CT), electroencephalogram, or routine neurological evaluations may be normal.

It is believed that the neuropathology of MTBI is predominantly a diffuse axonal injury (DAI) caused by shear forces in the brain caused by sudden deceleration. As demonstrated by Oppenheimer, microscopic lesions have been noted in the brain following head injury, where patients died of other causes. Earliest lesions have been detected 15 hours post-injury, and include microglial cell proliferation, petechial hemorrhages, and other signs of diffuse axonal injury. Following this neuroanatomic verification, reports of deficits in cognitive function of patients with MTBI (with grossly normal neurologic examinations) became more frequent in the literature in the 1980's.

Recent evidence from the Centers for Disease Control and Prevention (CDC) demonstrate a significantly higher incidence of MTBI than previously estimated (Langlois et al., 2005). These epidemiologic studies reveal that the number of patients admitted to hospitals for TBI is dwarfed

by the number who are treated and released from EDs. It is estimated that each year in the United States, MTBI accounts for about three fourths of the 235,000 TBI-related hospitalizations and almost all of the 1.1 million TBI-related ED visits without hospitalization. Due to the magnitude of this problem, even brief periods of disability resulting from MTBI could impose a significant economic burden (Boake et al., 2005).

As early as 1993, Kurtzke and Jurland estimated the annual incidence of MTBI as approximately 180 per 100,000 population. However, based on patients evaluated and discharged from the ED, the incidence of MTBI has been reported to range between 216 and 392 per 100,000 population. In a recent analysis of data from the National Hospital Ambulatory Medical Care Survey for 1998-2000, the average incidence of MTBI was found to be 503.1 per 100,000 population, significantly higher than previous estimates. Most of these figures may still underestimate the problem, as patients admitted to the hospital with, and tested for, MTBI probably represent only a proportion of the total who actually sustain MTBI. And many of those who sustain head trauma and do not present to a hospital initially are unlikely to report their injury at a later date unless residual cognitive, behavioral or physical symptoms impact their daily lives and employment.

The CDC (2003), has referred to MTBI as a “silent epidemic” because the problems experienced by patients with this injury are often not visible but may have profound consequences such as long-term physical, mental, social, or occupational sequelae (McCauley et al., 2001; Ruffolo et al, 1999). Due to the magnitude of this problem, in 1999 the National Institutes for Health (NIH) declared that efforts to reduce post-MTBI disability should be a national research priority. However, given the lack of effective treatments, these reduction efforts have focused mainly on primary prevention.

While only 1% of cases initially classified as MTBI are severe enough to require neurosurgical intervention (e.g., Jeret et al., 1993), considerable variability of injury severity can exist within this narrowly defined group. Huynh et al. (2006) conducted an archival study of 56 MTBI patients with GCS of 15 (64% motor vehicle crash (MVC) as mechanism of injury) and found a high incidence of both LOC and amnesia (88% and 78%, respectively). Furthermore, CT findings revealed that 43% of the sample had evidence of parenchymal contusion and 38% had evidence of subarachnoid hemorrhage. Eighty-four percent of patients showed no improvement on CT repeated 24 hours after admission. Therefore, even patients initially diagnosed with a "mild" head injury may experience complicated neurological and/or general physical injuries associated with poorer prognosis or functional outcome (Iverson, 2005). Conversely, other MTBI studies have used more conservative criteria for participant selection (e.g., Stapert et al., 2006) or have excluded participants with abnormal head CT (Sheedy et al., 2006). Variability in MTBI definition used and inclusion/exclusion criteria employed by researchers may create additional heterogeneity in published findings.

The consequences of brain injury include cognitive, physical and emotional or behavioral symptoms. Cognitive consequences can include short-term memory loss, slowed ability to process information, spatial disorganization, inability to do more than one task at a time, impaired judgment, difficulty concentrating, initiating activities or completing tasks. Physical consequences can include headaches or migraines, seizures, dizziness, double or blurred vision, muscle spasticity, fatigue, increased need for sleep, and balance problems. Emotional or

behavioral consequences can include increased anxiety, depression and mood swings, impulsive behavior, increased agitation, anger and irritability and egocentric behaviors.

Among persons with MTBI, a proportion will experience longer term post-concussive symptoms, including cognitive dysfunction, such as memory impairment and difficulties in attention and concentration. In addition, executive functioning skills such as problem solving, planning and organization are also frequently impaired following MTBI. Studies have also suggested that MTBI can be a risk factor for psychiatric disorders such as depression. Due to these problems, MTBI is frequently associated with social, family, and employment changes, thus impacting not only the individual but society in general.

Although it is difficult to predict how people will be affected by brain injury, almost all who have sustained a brain injury exhibit some of the above consequences. Each part of the brain has its own function; however, all parts work together and damage to one area may impact the function of others. These injuries may permanently alter occupational functioning and can have profound effects on the individual's social and family relationships. Residual cognitive impairments may result in the loss of communication skills, memory and an inability to organize tasks, solve problems or pay attention to details. In addition, TBI may cause emotional instability and changes in the ability to see, hear and smell (Thurman et al., 1999).

The presence of concomitant injuries also poses an issue for patients suffering from MTBI. Stulemeijer et al., (2006) reported that 44% of individuals suffering additional injuries continued to suffer functional disability 6-months post injury, compared to 14% of patients with uncomplicated MTBI.

Many studies of MTBI have been conducted in young, healthy males with sports-related concussions. These studies frequently have incorporated pre-season baseline screening as well as post-injury sideline and follow-up assessment. A summary of findings from some of these studies is presented later in this review.

Military Relevance of the Problem:

Those serving in the military have been shown to be at higher risk for TBI than the general population, in part due to rigorous training and combat situations. There are over 7,000 peacetime TBI admissions to Department of Defense (DOD) and Department of Veteran Affairs (DVA) hospitals each year. In addition to the costs of acute and long-term care, it is conservatively estimated that $30 million in obligated medical retirement payments is added each year from TBI in the military alone (Salazar et al., 2000).

Ommaya et al. (1996) reported on the causation, incidence and costs of TBI in the U.S. military medical system. Hospital discharge records from military and private facilities reimbursed by the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS) for fiscal year 1992 were reviewed to identify head injury admissions. The authors note that firearms and motor vehicle crashes caused the most severe injuries for cases admitted to military facilities. Military active-duty individuals were at increased risk for non-combat head injury. Eighty

percent of the total military facility cost for head injuries was attributable to motor vehicle crashes, falls, and fighting. CHAMPUS expenditures for rehabilitation of patients with head injuries are high, thus accentuating the need for data on the cost-effectiveness of TBI rehabilitation. The authors concluded that prevention of head injury in military settings should focus on motor vehicle crashes, fist fights, and falls.

In a subsequent study, the authors compared reasons for military discharge in a population of active duty personnel with and withoutTBI (Ommaya et al., 1996). When compared with the total discharge population, the relative risk for behavioral discharge was 1.8 times greater for those with MTBI (defined as maximum AIS(Abbreviated Injury Score) head equal to 1 or 2). In addition, those with MTBI had a discharge rate for criminal conviction 2.7 times that of the comparison population. Also, those with MTBI had an average of 8.5 total sick days (defined as the time from admission to return to duty or separation from service), with a standard deviation of 39.7 days. Thus, thousands of man-hours in experience and training are lost each year due to the effects of TBI in soldiers who are prematurely returned to active duty or separated from the service outright. The authors concluded that, while the most effective way to reduce the cost of TBI is primary prevention, secondary and tertiary prevention measures such as evaluation and rehabilitation, where indicated, should be undertaken on a routine basis, following TBI.

In a recent survey of active duty U.S. soldiers, it was reported that approximately 23% reported sustaining a TBI after joining the Army. Among paratroopers the incidence was approximately double, largely due to parachute-related injuries. In addition, paratroopers with a history of TBI before joining the Army had a significantly higher prevalence of TBI while in the Army than paratroopers with no previous history (Ivins, et al., 2003).

While much of the focus in the past has been on penetrating brain injuries, in the Iraqi conflict, concussive force seems to be a greater concern. This is thought to be due to several factors, including increased uses of explosive devices among insurgents, and sophisticated body armor that allow troops to survive attacks that were previously un-survivable.

Concussion can occur as a result of a blast injury to the brain. Previously, LOC and coup and contrecoup injuries were considered to be secondary or tertiary injuries, but with increased usage of body armor, damage to the central nervous system following an explosion has been increasingly attributed directly to the effects of the blast (DePalma et al. 2005).

Of the initial 433 patients seen at Walter Reed Army Medical Center from January 2003 to April 2005 (from Afghanistan and Iraq conflicts), almost half had sustained a MTBI (Warden, 2005). Sixty-eight percent of this group had injuries resulting from an explosion or blast, and 25% sustained a skull fracture. The majority (79%) sustained LOC of an hour or less, and 43% had post-traumatic amnesia of 24 hours or less. Ninety one percent reported some post-concussive symptoms.

Diagnosis and Presentation:

Mechanism of Injury:

TBI can be caused by several different physical mechanisms, with varying degrees of severity. One mechanism for sustaining TBI involves a direct blow, or impact, to the skull. These focal injuries (i.e. brain contusions) are believed to be caused by dilatational stresses that occur within the biphasic brain tissue. Cavitation injuries can occur at the point of impact (coup) or at the opposite side of the brain (contrecoup). If the blow results in a displaced skull fracture, an associated laceration of the underlying brain tissue may occur. Another mechanism of TBI involves the relative tangential displacement between the skull and brain at their interface. Large motions of the brain relative to the skull can lead to ruptures of the parasagittal bridging veins, which can cause bleeding between the skull and brain (epidural or subdural hematoma), or inside the brain material itself (intracerebral hematoma). An additional mechanism of TBI involves the over-stretching of the axons within the brain material. Large areas of high strain within the brain material are believed to be the cause of DAI, which is typically related to large rotational motions of the head. Severe cases of DAI can lead to permanent disability and prolonged coma. Mild cases of DAI are potentially reversible with prompt medical diagnosis and treatment. These types of severe brain trauma were not included as part of this research project. Instead, the focus was on mechanisms causing and outcomes from mild, closed-head TBI.

Brain concussion, the most common type of MTBI, is characterized by a transient LOC (less than 30 minutes) and/ or peri-traumatic (antegrade or retrograde) amnesia (less than 24 hours). Concussions typically have no visible lesions on brain CT. The organic bases of brain concussion are felt by some authors to be at the biochemical level (Gennarelli et al., 1982) or at the axonal level (Mittl et al., 1994). The latest type (microscopic axonal disruption) can be understood as the mildest form of DAI (Rees et al., 2003).

Diagnosis and Medical Management:

Since Level I trauma centers are viewed as leaders in the care of injured patients, a survey study was undertaken to characterize evaluation and treatment practices of MTBI patients in these clinical settings. The findings, based on responses from thirty-five centers in 24 states, revealed that less than half (45%) of centers currently formally evaluate all trauma patients with MTBI. Patients identified with MTBI discharged from the ED are referred for further evaluation at only 34% of centers. Furthermore, there is no consistent practice for determining which patients with MTBI are evaluated, what tools are used, or who performs the evaluations (Blostein and Jones, 2003).

Diagnosis of MTBI is difficult due to the frequent lack of objective evidence such as neuroimaging findings, and also due to the often non-specific nature of the symptoms, which can include confusion, difficulties with concentration, headache, dizziness, nausea and/or vomiting, or impaired coordination. Moreover, sensitive diagnostic tools or biochemical markers that correlate with symptom reports are still lacking (Borg et al., 2004). Neural mechanisms mediating the development of TBI symptoms remain poorly understood. Clinical signs and

symptoms may be related to a complex cascade of ionic, metabolic and physiologic events; this process may involve injuries to the axon, to neurons and glial cells, or both.

The Eastern Association for the Surgery of Trauma has developed practice management guidelines for the management of MTBI (Cushman, et. al., 2001). As part of their recommendations for Level III trauma hospitals, they reiterate the fact that "post-concussive symptoms include headache, dizziness, memory problems, and other symptoms that occur acutely in approximately 50% of MTBI patients and in 33% at three months from injury. These symptoms *may* identify a subgroup of patients at subsequent increased risk for prolonged cognitive deficits as a result of their injury." They further state that neuropsychological testing of MTBI patients in the acute care setting has been suggested to identify patients at high-risk for prolonged cognitive deficits, "however, it needs further study."

Post-injury complaints following MTBI are somewhat ambiguous, and variability may be related to issues such as delays in seeking treatment, health care professionals' lack of knowledge about diagnosis of MTBI, or symptom overlap with other diagnoses or conditions. Other factors that are thought to play a role are a heightened exaggeration of symptoms in order to gain from legal claims, or underlying mood disorders.

Sports-Related Studies of Concussion:

Several studies have shown that sports concussion is a serious public health problem (Collins et al., 1999; Matser, et al., 1999). Neuropsychological tests have been administered to cohorts of healthy athletes and then re-administered to those who subsequently sustain concussions, thus allowing for a determination of when and if a subject has recovered from a cerebral concussion. However, these populations are largely young males who have sustained isolated MTBIs, in contrast to both civilian and military populations, where TBI frequently results from motor vehicle collisions or falls, and associated injuries may also be present.

The majority of athletes who have sustained a concussion report posttraumatic headache. However, few studies have prospectively examined the association between post-concussion headache and neurocognitive impairment, and other post-concussive symptoms. Collins et. al. (2003), addressing this lack, conducted a follow-up study of 109 high school athletes sustaining concussion. Their findings suggest that high school athletes with any reported degree of headache at one week post-injury are more likely to have persistent adverse affects. Furthermore, it was apparent that headaches rated moderate-to-severe may be associated with even worse neurocognitive status, although the sample sizes were too small to adequately address the question. Athletes were only followed for one week, but the presence of post-concussion headache at approximately 7 days post-injury was associated with a larger number of post-concussion symptoms other than headache. Players reporting posttraumatic headache also had significantly worse performance on reaction time and neurocognitive measures of memory.

Post-concussion syndrome (PCS) has significant implications, especially for athletes, due to the presence of cognitive impairments that may slow reaction time and/or information processing speed. Currently most concussion guidelines for athletes predicate return to play on the presence

and duration of LOC or amnesia. However, neither of these symptoms needs to be present for an injury to be classified as a concussion. In fact, based on a recent study of high school and collegiate football players, LOC and amnesia occurred relatively infrequently, in only 9% and 28% of concussion cases, respectively (Guskiewicz, et al, 2001).

As pointed out by Collins et al. (2003), "somewhat disconcerting, however, is that no prospective study has examined whether post-concussion headache is associated with neurocognitive impairment and presence of other post-concussion symptoms", thus suggesting incomplete recovery. "Moreover, neither headache nor even general clinical outcome in sports-related concussion in high school athletes has been studied."

The decision about when to return to play, for those with sports-related MTBI, has been addressed by several authors. The goal of the resultant guidelines has been to prevent more serious brain injuries by identifying high-risk subjects. Bailes (2001) recommended a management scheme for athletes with concussion based on a modification of the Colorado Medical Society Guidelines for the Management of Concussion, guidelines from Cantu (2001), as well as his own experience. The following guidelines grade concussions as mild, moderate, or severe, and assume that the subject is asymptomatic prior to return to play.

Grade 1 (mild). Confusion with no amnesia or LOC. If confusion clears within 20 to 30 minutes, then allow return to play, otherwise, may return within one week of being asymptomatic. After a second mild concussion in the same season, do not return to play for 2 weeks; must be asymptomatic at least one week and have a normal CT scan. Terminate season if a third mild concussion occurs. Return next season if asymptomatic.

Grade 2 (moderate). Confusion with amnesia, no loss of consciousness. May return to play only after appropriate evaluation and asymptomatic for one week. After a second moderate concussion, may return to play only after asymptomatic for one month and CT scan documented to be normal.

Grade 3 (severe). Any LOC. Urgent transport to hospital for evaluation and CT scan. May return to play after asymptomatic for at least two weeks, if LOC < 1 minute and CT scan is normal. For LOC >1 minute, do not return to play for at least one month.

TBI, Stress and Post-traumatic Stress Disorder (PTSD):

Based on the poor specificity of neuropsychological testing (in differentiating the origin of the deficit) and the lack of evidence of a connection between persistent PCS and an organic sequela of TBI, it has been hypothesized that injury to the limbic circuitry of the hippocampus caused by the initial TBI and reinforced by a maladaptative neuroendocrine stress response could be at the core of the neurocognitive and emotional symptomatology of persistent PCS patients (Rees et al., 2003).

Report of anxious mood may also be a common consequence of TBI. Estimates in the literature indicate that approximately 24% of individuals may be diagnosed with an anxiety disorder following injury compared to 3% pre-injury (Mooney & Speed, 2001). Due to the nature of

traumatic injury, acute stress disorder may persist to the development of PTSD. Levin et al. reported a PTSD prevalence rate of 13% in a MTBI sample 3-months post-injury. At 6-months post-injury Bryant and Harvey (1999) reported that that 24% of their MTBI sample met criteria for PTSD and 22% continued to meet criteria at 2-years post-injury. While the amnesia and LOC characteristic of brain injury may seem protective against the development of PTSD, researchers have argued that islands of memory can exist during PTA and that traumatic memories may not be verbally accessible (Moore et al., 2006; Joseph & Masterson, 1999). Taken together, it is clear from the literature that patients with MTBI may experience a variety of anxiety and mood symptoms post-injury that can impact long-term functioning.

Outcomes of Mild TBI:

Overview:

The CDC has estimated that 5.3 million U.S. citizens (approximately 2% of the population), are currently living with disability resulting from a TBI. However, this estimate does not include those who were not originally admitted to hospitals (i.e. treated in EDs or as outpatients), so this is acknowledged to be an underestimate of the problem.

The medical and public health literature has increasingly addressed the persistence of adverse outcomes among patients with MTBI. However, despite the interest in the subject (the World Health Organization has identified more than 38,800 references on mild TBI published from 1980 through 2001), fewer than 430 articles focused on prognosis or outcomes of persons with MTBI; in addition, among this group there was such variability in analytic approaches, that it was not possible to pool data for analytic purposes. However, despite these problems, available evidence did indicate that cognitive deficits and symptoms occurring within the initial days following injury were frequently resolved within a few months.

Post-Concussive Syndrome:

The etiology of PCS currently remains subject to debate as routine neuroimaging methods appear insensitive to structural changes in the brain which may account for persistent symptoms. Some researchers believe that psychological factors, such as coping style or the psychological effects of trauma may best account for PCS (Bryant & Harvey, 1999; Landre et al., 2006). Litigation status also has been shown to be associated with persistent symptoms in some investigations (e.g., Chan, 2005b).

In recent years, extensive studies have been conducted to document the cognitive, emotional, and functional effects of MTBI, and to describe the natural history of the injury. Chambers et al.(1996) noted that even in patients thought to be at low risk for having any degree of TBI (no imaging documenting or suggesting TBI, a negative neurologic examination and discharged home from the ED), the incidence of symptoms suggestive of PCS was 32% at one month post-injury and 17% at 2 months. Moreover, 7% of all patients discharged from the ED had not resumed their normal daily routines at 2 months post-injury. Other studies have identified injury-related factors such as LOC and posttraumatic amnesia, as well as other variables that might be predictive of outcomes. However, few studies have included objective empirical data

on the immediate neurocognitive effects, and how these findings might assist with identification of which patients with MTBI will have more long-term or persistent symptoms.

MTBI is known to have consequences on cognition. Immediately after sustaining MTBI, an individual may feel dazed, confused, or disoriented and experience disrupted memory. Cognitive difficulties may continue anywhere from minutes to days post-injury. While the severity of impairment may vary according to the definition of MTBI used and other personal characteristics such as demographics (Dikmen et al., 2001), initial cognitive deficits typically include complex attention, processing speed (e.g., simple and complex reaction time), non-verbal fluency, memory, and executive function (Alexander, 1995; Bleiberg et al., 2000; MacFlynn et al., 1984; Frencham et al., 2005; Mathias et al., 2004; McAllister et al., 2001; Brooks et al., 1999). While LOC is commonly used to assess severity of injury and may be associated with increased distractability and/or impulsivity (Brewer et al., 2002), it does not appear to be associated with greater impairment on neuropsychological assessment in MTBI (Iverson et al., 2000; Leininger et al., 1990).

At least four recent meta-analyses of the literature on the nature and course of neuropsychological impairment have concluded that these initial cognitive symptoms typically resolve by approximately 3 months post-injury (Binder et al., 1997; Frencham et al., 2005; Schretlen & Shapiro, 2003; Belanger et al., 2005). Binder and colleagues' (1997) analysis included a total of 11 samples of participants more than 3 months post-injury, selected solely on the basis of history of MTBI (rather than complaints of persistent symptoms). A small overall effect size was obtained (0.12, $p<0.3$) with attention being the most affected neuropsychological domain ($d=0.20$). Frencham et al. (2005) analyzed data from 17 additional studies published since Binder et al.'s report. Their results indicated a significant effect of MTBI on attention/working memory and processing speed. Small effects on memory and executive function were also noted in the acute phase (<24 hrs post-injury). However, these relationships decreased to non-significant levels when it was the post-acute phase of recovery under examination.

Schretlen and Shapiro (2003) sought to estimate the course of cognitive recovery by conducting a meta-analysis of available cross-sectional, unselected samples. They compared recovery course of those with MTBI to individuals sustaining moderate-to-severe brain injuries. Thirty-nine studies from 1984-2003 were included for a total patient *n* of 1716 (control subject *n*=1164). The effect size of cognitive impairment across all time points (<7, 7-29, 30-89, >89 days) for patients sustaining MTBI was $d=-0.24$, compared to $d=-0.74$ for moderate-to-severe patients. The effect was largest at <7 days post-injury ($d=-.41$), but this translated to scoring at the 33rd percentile compared to controls (i.e., still within normal limits). By 30-89 days post-injury, the effect of MTBI on cognitive impairment was no longer significant. In order to infer recovery course from their data, an analysis of correlations and effect sizes of impairment over the first 2 years was also conducted. The authors concluded there was strong evidence to support an exponential recovery course from MTBI. On the other hand, the performance of moderate-to-severe TBI patients continued to differ from controls at every time point included in their analysis.

A more recent meta-analysis, conducted by Belanger and colleagues (2005), attempted to calculate effect sizes by cognitive domain because overall estimates of neuropsychological impairment may obscure small, but important, differences specific to MTBI. Using data from 39 studies conducted between 1970 and 2003, the largest effects on cognitive function for unselected samples were observed for language fluency and delayed memory at <90 days post-injury. Motor and executive function were domains least affected by MTBI. The authors also examined potential moderators such as litigation. Both unselected and litigation samples had similar overall effect sizes at <90 days. However, at an average of 13 months post-injury, effect of MTBI on cognitive impairment increased in the litigating samples, a trend opposite to that of unselected samples. Poor effort or symptom exaggeration could not fully explain the effect of litigation on cognitive impairment 90 days post-injury. Thus, the results of Belanger et al. confirmed conclusions of prior meta-analyses that most individuals suffering MTBI can expect a full recovery by 3 months post-injury.

Studies tracking post-concussional symptoms (Ingebrigtsen et al., 1998; Martelli et al., 1999; Alexander et al., 1995) suggest a complex mixture of cognitive, behavioral, and physical symptoms were present in patients with MTBI at 3 and 6 months post-injury. Although recovery time varied considerably among individuals, most appeared to enjoy a complete resolution of their post-traumatic symptoms. However, others report persistent problems that are often subtle and go undetected and are difficult to verify. Accurate identification of post concussion symptoms is important in mitigating long-term problems.

Ponsford and his group investigated the outcome from mild head injury in adults (N=84) at one week and three months post injury (2000). At one week post injury, patients with MTBI were reporting headaches, dizziness, fatigue, visual disturbances, and memory difficulties. At three months, symptoms reported at one week had largely resolved. However, a subgroup (24%) still suffered many symptoms resulting in a significant disruption to their daily lives.

Van der Naalt and colleagues (2000) observed a prospective sample of patients with mild to moderate head injury for frequency of behavioral disturbances. Forty percent of patients reported restlessness and 19% reported agitation. Additionally, patients with behavioral disturbances had twice as many lesions (81% compared with 39%) in the fronto-temporal regions on imaging studies. In two-thirds of patients with early behavioral disturbances, residual emotional and cognitive impairments were seen at one year after the injury.

Neurobehavioral symptoms are common immediately after a minor head injury; however, few studies have examined the effects at one year. Deb, Lyons, and Kourzoukis (1998) estimated that rate and pattern of neurobehavioral symptoms in 196 patients. One year post-injury a significant proportion of the group had 3 or more symptoms, with 35% having symptoms of irritability, 15% lack of initiative, and 3% social disinhibition. Pre-morbid factors such as lower social class, lower educational achievement, and post-injury factors such as GCS and presence of disability influenced the rate and pattern of behavioral symptoms.

Prognostic Studies:

Studies To Predict Post-Concussive Syndrome (PCS) -- There is an urgent need to be able to predict which patients with MTBI will experience long-term or persistent symptoms. Such knowledge would be useful for several reasons. First, risk stratification would be important for ED clinicians, in order to help decide who should seek specialized follow-up care. This information could also guide decisions about return to sports or military duty, in patients who have suffered a mild TBI. In addition, identification of the patients at high risk for post-concussive symptoms would assist with further research to determine whether early intervention might prevent or reduce the duration of such symptoms.

Conceptually, post-concussion symptoms remain problematic because they are not specific to head injury (e.g., also observed in chronic pain and PTSD), are present to some degree in healthy individuals, and are affected by one's expectations and attributions following injury (Smith-Seemiller et al., 2003; Chan, 2005b; Ferguson et al., 1999). Alfano & Satz (2000) have urged that future studies investigating PCS in head injury should utilize two control groups whenever possible (i.e., other injury and no injury groups) to better determine if PCS is related to physiological effects of MTBI or if these symptoms reflect consequences of general physical injury. Although many of these symptoms are relatively non-specific, in a recent case/control comparison of patients with and without MTBI, symptoms, medical services use, and social and employment concerns were evaluated 6 months post-injury. Headaches, dizziness, vision difficulties, memory or learning problems, and alcohol intolerance were found to occur significantly more often in the MTBI cohort than in the comparison group. (Kraus et al., 2005)

However, the utility of PCS as a predictor of persistent cognitive and functional impairment following MTBI is likely to remain difficult due to the lack of specificity of the most common symptoms (e.g., headache & dizziness) and the rarity of persistent symptom constellations (Alves et al., 1993).

Currently, few studies have utilized standardized screening techniques or followed patients over time. Logistical constraints in the ED or trauma care setting significantly limit the opportunities for prospective research and the ability to use standardized methods for assessment of MTBI during the acute phase. Thus, the use of standardized neuropsychology methods beyond the traditional injury classification methods is quite uncommon, primarily due to time and staffing constraints encountered in acute care settings. Commonly used scales such as the GCS have been shown to correlate well with neuropsychological and psychosocial outcomes after more severe TBI, but are not sensitive to the more subtle neurocognitive changes that may be the result of MTBI. Thus, neuropsychological screening may be a better way to identify and characterize long-term effects, especially cognitive and behavioral in nature.

Findings from studies designed to predict Post-Concussive Syndrome among subjects with mild TBI are summarized below:

Glasgow Coma Scale(GCS). It is difficult to predict which patients with MTBI will have ongoing cognitive, emotional, or physical symptomatology. The GCS is widely used to classify

degree and severity of head injury, based on initial behavioral and motor responses following injury. However, the GCS is intended primarily to provide a measure of depth of coma in the first weeks post-injury, and thus does not adequately capture changes in mental status associated with MTBI. McCullagh et al. (2001) showed that, despite early neurosurgical differences in patients with admission GCS scores of 13-14 vs. 15, GCS scores did not clearly translate into neuropsychiatric sequelae at 6 months post injury.

Computed tomography (CT) scanning. CT scanning also does not predict symptoms among patients with MTBI. Hanlon et al. (1999), in a study of vocational outcome following mild traumatic brain injury, found significant differences between subgroups of patients classified by (1) mechanism of injury (acceleration/deceleration striking object, etc.) and, (2) type of injury (motor vehicle collision, fall, assault, etc.). However, there was no difference, with respect to neuropsychological status or vocational outcome, between patients who had findings on CT versus those who were CT negative. In addition, there were no differences between patients who had suffered a brief LOC and those without LOC.

Grosswasser et al. (2002) retrospectively examined radiologic predictors of long term work outcome for war-injured veterans 12-14 years post penetrating head injury. They found that widening of the third ventricle (>7mm) was the best radiologic predictor of future work status. However, overall empirical support for the predictive value of brain imaging remains mixed (Asikainen, et al., 1996; Sherer et al., 2002). Thus, having reliable, sensitive, and objective techniques to evaluate outcome from MTBI would not only enhance understanding of the range of residual problems from mild head injury, but would also improve prediction of outcome and patient management during the recovery interval.

Injury Mechanism. Regarding mechanism of injury, findings were again mixed. Hanlon et al, (1999) found that MTBI outcomes differed by mechanism of injury; injuries involving an object striking the head (e.g., assault) were associated with poorer employment outcome than acceleration/deceleration injuries. In addition, Groswasser et al. (2002) found war-injured veterans who sustained a closed head injury were more likely to return to work than those with a penetrating head injury. Other studies found no empirical support for an association between mechanism of injury and employment outcome (Sherer et al., 2002; Greenspan et al., 1996; Kreutzer, et al., 2003).

Balance Testing. No reports of the results of balance testing as a predictor of future functional status following MTBI have been found in the literature. One study of severe head injuries, using the Neurocom Balance Master, does show few correlations between neuropsychological test variables and balance measures, suggesting that balance and neurocognitive impairment are separate constructs that need to be addressed individually (Mullin et al., 2002).

Cognitive Testing. In a recent review article, there were 66 studies related to prognosis of MTBI in adults, ten of which related to injuries sustained in sports. Several studies, using formal cognitive assessments, have noted sound evidence of cognitive deficits within the first few days following injury, including problems with speed of information processing, attention, and recall of material. There are also consistent findings that early cognitive deficits in MTBI are largely resolved within a few months post-injury, with most showing resolution within three months.

None of the studies noted an association between LOC and increased deficits in cognitive functioning following MTBI.

Physical Symptoms. De Krujik et al. (2001), in a study of 107 patients admitted to an ED for initial treatment, reported that the initial presence of headache, dizziness, and drowsiness in the ED was associated with increased symptoms at the 6-month follow-up evaluation. Another study looked at vestibular dysfunction, a commonly reported set of symptoms following mild head injury. Vestibular dysfunction, expressed as vertigo, dizziness and imbalance, can be seen in the full spectrum of head injury. It is one of the recognized symptoms of the post-concussion syndrome and is a common, persistent sequela of more severe forms of traumatic brain injury (Levin et al., 1989).

Biomarkers. In terms of biochemical markers for TBI, only three studies to date have found S100B to predict outcome among MTBI patients. Townend (2006) found a correlation between S100B and outcome using the extended Glasgow Outcome Scale (GOS) and predicted severe disability at one month with a sensitivity of 93% and a specificity of 72%. Stranjalis (2004) found S-100β levels to be associated with lower early (one week) return to work or activities. Also a report by Stalnacke (2005) found an association of S-100β with disability and low life satisfaction at one year follow-up.

Early predictors of PCS at 1-month follow-up included poorer memory and information processing speed, balance scores, and acute pain reported at emergency room assessment (Sheedy et al., 2006). Risk factors for persistent symptoms beyond 6-months include age (>40), lower socioeconomic status, female gender, alcohol abuse, prior head injury, and multiple trauma (Evans, 1992). PCS has been associated with impairment in divided and sustained attention at 6-months post-injury (Bohnen et al., 1992; Bohnen et al., 1995). Evidence of intra-cranial injury on CT has also been associated with persistent headache and memory difficulties at 1 year post-injury (Sadowski-Cron et al., 2006). In prospective studies of MTBI (Alves et al., 1993), PCS symptoms typically show significant reductions during 1-year post-injury, with the most common persisting symptom being headache. Patients that experience persistent PCS may have heightened sensory sensitivity and poor modulation of sensory phenomena, which may impair information processing and disrupt higher order processes such as attention, memory, and executive function (Kumar et al., 2005).

Studies of Return to Work--MTBI has been associated with a range of psychosocial and functional outcomes. Loss of productivity following MTBI contributes to significant financial and social burden. Return to work has most commonly been used as an index of successful rehabilitation with regard to functional outcome. The importance of work to the psychosocial adjustment of individuals who sustain TBI has been well established in the literature. A large range of variables relevant to employment outcome has been examined in the literature including demographic information, injury data, neuropsychological measures, environmental, and psychosocial factors.

Predictors of outcome related to the individual's injury include overall functional status, severity of injury, mechanism of injury, and head imaging data (Ownsworth and McKenna, 2004). Strong empirical support exists for the predictive value of functional status (e.g., physical

disability, cognitive impairment, psychosocial adjustment, independence) at time of discharge on employment outcome (Sherer, et al. 2002; Greenspan et al, 1996; Kreutzer et al., 2003; Ponsford et al., 1995; Malec, 2001). Boake and High (1996) found that multidimensional measures of functional outcome were more sensitive in predicting outcome than uni-dimensional measures. Additionally, Gurka et al., (1999) found that the combined use of two different but related functional outcome measures improved the prediction of work status. Findings from these and other studies (Ownsworth, et al., 2006) suggest the assessment of a broad range of skills to enhance the ecological validity of its use to predict work outcomes. LOC, post traumatic amnesia (PTA), and GCS were the most common indices of injury severity examined in the literature (Ownsworth and McKenna, 2004; Sherer et al, 1999). All three indices were inconsistent predictors of employment outcome. Bowman (1996) noted that severity of injury may be a more reliable predictor of survival and neuropsychological functioning than psychosocial outcomes.

Ownsworth and McKenna (2004) conducted a comprehensive literature review on factors consistently associated with employment outcome following TBI (mild, moderate, and severe). A number of demographic factors have been associated with work status following injury. Specifically, there is consistent empirical support regarding the relationship between pre-injury occupational status and employment outcome; those with higher qualifications (e.g., skilled vs. unskilled professions) before injury are more likely to return to competitive employment after injury (Klonoff et al., 2006; Walker et al., 2005). Similarly, Boake et al. (2005) found that patients with higher job status tended to return to work earlier. These findings are also consistent with previous meta-analytic findings (Crepeau and Scherzer, 1993).

There was also evidence for an association between race/ethnic identity and employment outcome; African-Americans and other minorities are approximately twice as likely to be non-productive than Whites post injury (Sherer et al., 2002). However, the authors noted the importance of systematically controlling for potentially confounding variables (e.g., level of education, pre-injury work status). The literature is mixed regarding age as a predictor for vocational outcome. However, in general, it appears that those injured at either very young ages or at 40 years and over are less likely to return to work (Keyser et al., 2002; Ponsford et al., 1995).

Findings were mixed also regarding education, marital status, (Wood and Yurdakul, 1997; Klonoff, et al., 2006) premorbid psychological adjustment or substance abuse, and work outcome. Gender was not found to be a significant predictor of return to work (Klonoff, et al., 2006). Finally, there was insufficient research on socioeconomic status to allow comment on its value as a predictor of employment outcome (Ownsworth and McKenna, 2004).

Sherer et al (2002) reviewed 23 studies regarding the relationship between neuropsychological test results and employment outcome after TBI. Results of the review recommend the use of early neuropsychological assessment to predict late employment outcome. Studies of late or concurrent neuropsychological assessment and subsequent employment were inconclusive with regard to utility of neuropsychological assessment to predict outcome. Further, there is moderate empirical support for the predictive value of global cognitive indices (Dikmen, et al., 1994; Sherer, et a., 2002) on employment outcome. There is also moderate empirical support for the

predictive ability of measures of visuo-spatial abilities (Boake, et al., 2001; Bowman, 1996). In addition, executive functions were the most reliable neuropsychological indicator associated with employment outcome. One criticism noted by Burgess et al. (1998), however, is that there may be little correlation between an individual's performance on a test of executive function administered in a standardized testing situation and his performance in a real world setting. As such, there has been a push for developing tests with increased ecological validity. Findings are inconclusive with regard to the predictive value of estimated pre-morbid IQ, verbal/language functioning, memory functioning, and attention/processing speed on employment outcome.

Regarding psychosocial factors, there is moderate support for the relationship between emotional status and return to work following injury. Ruff et al (1993) found that individuals with higher levels of depressive symptoms at 6 months post injury were less likely to be employed at 1 year post injury. There is insufficient research or inconclusive findings regarding the predictive value of interpersonal skills, posttraumatic stress, self-reported symptoms, or self-awareness on post injury employment outcome.

In a recent study, Chamelian and Feinstein (2004) reported that dizziness in those with mild-to-moderate TBI was an independent predictor of failure to return to work when assessed 6 months post-injury. Headache alone after mild TBI has also been associated with poor outcome (de Krujik et al., 2002). Headaches after TBI may have acute or delayed onset and are associated with more emotional distress, although, as reported by Walker et al. (2005), a prospective study of this relationship is lacking.

Reitan and Wolfson (1999) have demonstrated that, while MTBI patients with persistent complaints comprise a minority of the MTBI population, they evidence genuine impairment in neuropsychological functioning that may be missed in large, unselected-sample, investigations. For instance, Reitan and Wolfson compared a group of patients initially classified as MTBI, but who returned to the hospital with persistent cognitive and physical complaints, to a group of MTBI patients without persistent complaints. Seventy-five percent of those with continued complaints scored in the impaired range on formal cognitive assessment (compared to 39% of MTBI without persisting complaints and 89% of patients with definite brain injury). Therefore, patients with PCS may have suffered a more complicated injury with consequences more consistent with moderate brain injury, rather than MTBI. Based on their work comparing cognitive performance of MTBI groups with and without PCS, Sterr et al. (2006) have shown that PCS, rather than merely the experience of MTBI, is a more useful predictor of future cognitive impairment. On the other hand, one investigation of initial impairment (5 days post-injury) has shown that MTBI patients with PCS differ from those without PCS more with respect to psychological factors rather than in neuropsychological performance (Meares et al., 2006). Psychological factors appear to be implicated in both the development and maintenance of PCS and should be taken into consideration in future studies.

Ruffolo and colleagues examined relationships between injury severity and return to work (Ruffolo et al., 1999). Fifty patients were assessed within one month of injury and then at 6 and 9 months. Of the 42% who returned to work, only 12% resumed their premorbid level of employment and 30% returned to modified work.

In another outcome study aimed at determining the timing of athletes' return to play following mild head injury, Guskiewicz and colleagues obtained data on two measures, postural stability and cognitive function (Guskiewicz et al., 1997). They assessed postural stability using Sensory Organization Test on the NBM and various cognitive function tests. The athletes demonstrated increased postural instability until 3 days post injury. Additionally, the post-concussional signs followed the recovery curve for postural stability. In contrast, no differences between controls and athletes were noted in the cognitive performance. The authors raised the issue that these tests may not have been sensitive enough to reveal cognitive deficits.

SCREENING TESTS FOR MTBI IN THE CURRENT PROJECT:

The purpose of the current study was to conduct baseline cognitive, blood, and balance testing on a cohort of patients with mild TBI, in order to determine which factors distinguish those patients who go on to develop persistent symptoms at 3, 6, and 12 months intervals post-injury.

Cognitive Testing

Although symptoms following MTBI are variable in nature, deficits in executive function are common and have been well documented. These functions involve those capacities that enable one to engage in purposeful, self-serving independent behavior. Executive functions refer to a variety of different activities, all of which are presumed to be mediated by neuronal systems that include the prefrontal cortex. The prefrontal cortex is the part of the brain that is crucial to the control of all basic and cognitive activities, including language.

Speech-Language Pathologists conduct acute screening on MTBI patients in many trauma centers as part of the discharge planning process, but there are no reports relating findings from these tests to long-term symptomatology in a population of prospectively-followed patients. This is likely due to the fact that the testing can be quite time-consuming, standardization of brief cognitive screening has not been documented in the literature and clinical staffing patterns limit feasability in the clinical acute care setting. (Duff et al., 2002)

For the current study, the SCATBI (Scales for the Cognitive Assessment of Traumatic Brain Injury) was utilized to screen patients at several time intervals**.**

Neuropsychological Testing

The ANAM, including the ARES (ANAM Readiness Evaluation System), and Word Memory Test (WMT) constituted the Neuropsychological battery of tests designed to measure cognitive, emotional, and motivational functioning for the present study.

The Automated Neuropsychological Assessment Metrics (ANAM) was originally developed to monitor human performance changes in individuals with environmental challenges, but has increasingly been used in the clinical area to screen patients at risk of neurocognitive impairment. As a computerized screening tool, it is much more efficient than the more time-

consuming traditional methods of neuropsychological assessment. In addition, the ANAM is designed for repeated evaluations (Kane, et al., 2007).

The ANAM is a computerized battery of neuropsychological tests developed to permit highly accurate measurement of simple and complex reaction time. It was developed through the Office of Military Performance Assessment Technology, and consists of a number of distinct tests assessing different neurocognitive domains. The ANAM has been used in numerous studies of TBI (Bleiberg et al., 1997; Bleiberg, Halpern et al., 1998, and Daniel et al., 1999). A factor analysis of the ANAM vs. a set of traditional clinical neuropsychology tests used in MTBI indicated strong concordance between the computerized and traditional neuropsychological measures, supporting the construct validity of the ANAM.

ANAM is also able to discriminate between concussed subjects with and without a history of prior concussion, at baseline assessment prior to secondary injury and at post-injury follow-up (Warden et al., 2003). Recent studies of MTBI have demonstrated the significance of reaction time differences of 200 ms or less. Bleiberg et al. (2000) showed that the complex reaction time tasks in the ANAM battery successfully discriminated concussed from control subjects.

ARES (ANAM Readiness Evaluation System) development resulted from a need for a portable automated neurocognitive testing system that could be used in field medical setting such as Iraq and Kosovo (Proctor et al., 2002, 2003). Activity Research Services (ARS) was contracted by the Military Operational Medicine Program of the U.S. Army Medical Research and Materiel Command to develop a version of the ANAM test system for use on a personal digital assistant (PDA). This effort was carried out in conjunction with the ANAM software development team at SPAWAR in Pensacola Florida. The resulting instrument is the ARES (Elsmore and Reeves, 2004). It provides an inexpensive and portable testing platform for field and clinical applications, and test batteries can be configured from a library of tests derived from the ANAM test system.

The Word Memory Test - Recent investigations illustrate the importance of considering level of effort put forth by patients during neuropsychological testing. More specifically, many studies have documented high rates of exaggeration of cognitive impairment in MTBI patients who are seeking compensation (Binder, 1993; Grote, Kooker, and Garron, et al., 2000; Larrabee, 2000). In a recent study, Green (2007) found that as effort decreases, scores on most tests of cognitive functioning also decreased significantly and systematically. The failure to consider that some individuals do not provide adequate effort during testing may lead to incorrect conclusions regarding outcomes (e.g., diagnosis, treatment) in both research and clinical settings.

The association between poor effort and poor performance on tests of neurocognitive functioning has been found in several studies using a variety of measures of ‘effort’, including WMT. The WMT is an effort measure that was designed to detect deliberately poor performance during neuropsychological testing. The WMT was designed to test the exaggeration of memory difficulties and as such the components are sensitive to poor effort but insensitive to all but the most extreme cognitive impairment. The test has been validated in populations of TBI and other neurologic disorders (Green, 1996, 1999).

Green, Iverson, and Allen (1999) examined a large sample of patients involved in head injury litigation on the WMT and found that patients with less severe injuries performed significantly worse on the WMT measures of biased responding (i.e., malingering) than their moderately to severely injured counterparts. They also found, as expected, that significantly higher scores on all three WMT measures (Immediate Recall, Delayed Recall, and Consistency) were insensitive to brain damage. If scores on the WMT effort measures reflected true differences in levels of cognitive ability, lower WMT scores would have been associated with increased severity of injury.

Green, Rohling, Lees-Haley, and Allen (2001) examined 904 patients (including 470 with head injuries) in the context of a worker's compensation claim. Findings indicated that effort had a greater effect on test scores than severeTBI; specifically, the WMT explained more variance in outcome following brain injury than injury severity. Green (2007) again found that the variable of effort had more impact on test scores than severe TBI. The authors suggested that their data illustrate the importance of measuring and controlling for sub-optimal effort in both clinical and empirical research, particularly in similar populations.

A recent study by Bowden, Shores, and Mathias (2006) re-examined the conclusions made by the Green et al. (2001) study described above. Green and colleagues concluded that a larger proportion of explained variance produced by the WMT is evidence of its validity. However, Bowden and colleagues suggest that the validity of the WMT as a measure of effort implies an interaction between effort and injury severity on outcome scores. Their data did not find such an interaction in a sample of 100 TBI litigants and thus, concluded that their data do not support the view that effort, as measured by the WMT, interacts with injury severity to suppress cognition following brain injury. Evidence consistently suggests the need to assess effort particularly when examining TBI populations; however, there is a continued need for research in the utility of the WMT in such cohorts.

Balance

Balance disturbances, neuropsychological compromise, and impaired coordination are common complaints following MTBI (ICD-10 International Classification of Diseases, 10th ed; Ryan, 1992). Disordered balance following TBI has been reported in the literature, but has been defined in multiple contexts, including deficits of motor performance, subjective complaints of dizziness and disorientation, and/or the results of laboratory or other subjective tests. These symptoms are present in as many as 70% of people following TBI (Black et al 2000) and often result in long term functional deficits in stability and the ability to work and interact in the normal environment (Ropper & Gorson, 2007; Basford et al., 2003 Black et al., 2000; Ryan et al, 1992). Balance, neurocognition, and coordination are important components of clinical assessment because they are indicators of long term outcomes and fall risk following TBI (Mullin et al, 2002).

The etiological factors that result in balance disturbance following TBI are heterogeneous, and can result from a disruption of one of several systems, including the inner ear, the visual pathways, proprioception, the cerebellum, and the motor system (Black et al., 2000). Some have suggested that balance disturbance after TBI is diffuse in nature, resulting in a decreased speed of processing of balance-related information secondary to "slowness of subcortical activity and

spatiotemporal disruption of postural responses" (Geurts et al., 1996). Standing balance could be affected by disruption of these systems, resulting in difficulties in the timing and activation of muscle contractions, which in turn affect standing balance (Wade et al., 1997). Thus, this wide range of etiological factors may make it difficult to establish a clear relationship with neurocognitive factors.

Balance dysfunction has commonly been assessed crudely through clinical judgments about the qualitative aspects of postural sway (e.g., Rhomberg maneuver) or through subjective patient reports that failed to capture the nature of imbalance. An improved technique for quantitative assessment of the postural control system is available through use of force plates that enable precise measurement of the postural sway. Such systems typically derive indices of sway from measuring displacement of the center-of-pressure (COP) at the feet while the patient stands on the plate (Ingersoll et al., 1992).

The NBM (Neurocom International, 1999) attempts to provide a multifactorial, integrated assessment of the inner ear, visual pathway, proprioception, the cerebellum and motor system components of balance. Any one or more of these systems may be disrupted following TBI (Black, 2000). The Neurocom system provides standardized, computer-based assessments that measure the patient's response to the microsecond. This level of accuracy provides for a more detailed and objective measurement of balance disturbance following TBI and thus may have the potential to help identify those patients with long-term post-concussive symptoms. Reliability, sensitivity and validity are established for the NBM system and it has been found to be a useful predictor of the length of rehabilitation and psychosocial and vocational outcomes. (Mullin et al., 2002). A significant drawback for its use in field tests for balance and outcome following TBI is that the NBM is a large piece of equipment that cannot be easily moved from a controlled situation (Mullin et al., 2002).

In a study aimed at determining the timing of athletes' return to play following mild head injury, Guskiewicz and colleagues (2001) obtained data on two measures, postural stability and cognitive function. Postural stability was assessed using the Sensory Organization Test on the NBM, and subjects were also given various cognitive function tests. The athletes demonstrated increased postural instability until 3 days post-injury.

The Balance Error Scoring System (BESS) requires very little equipment (stop watch, 46 X 46 X 13 cm medium density foam surface (Exertools, Inc, Santa Clara, CA) and can be used in a variety of settings as a clinical field test of postural stability and balance (Riemann & Guskiewicz 2000; Wilkins et al 2004; Guskiewicz et al., 2001). In this test vision is eliminated while balance is assessed during bilateral, unilateral, and tandem stance first on the level and then on foam. Good inter-tester and intra-tester reliability and validity compared to the NBM has been established for the BESS (Valovich 1996; Rieman and Guskiewicz 2000).

As with other measures, balance is impacted by fatigue. Patients admitted to a trauma center undergo sleep disruption due to the timing of injury, transportation to the trauma center, vital signs monitoring, noise, necessary medical tests, hospital transportation, time in the operating room (OR) and recovery. Also, medication for sedation or pain can affect concentration. Due to travel time and time spent waiting for medical appointments, fatigue could play a factor in the

results of the balance assessments. Hydration and prior exertion levels also can affect balance (Wilkins et al., 2004). Because postural stability depends on integrating the somatosensory, visual and vestibular systems; fatigue, whether central or localized, will likely affect balance (Wilkins et al., 2004; Black et al., 2000).

Fatigue is reported to significantly increase errors in BESS assessments, particularly in tandem stance, while rest, practice and learning have improved BESS scores (Wilkins et al., 2004; Mancuso et al., 2002). Similarly, fatigue is reported to decrease postural stability as measured by the NBM except during fixed support with the eyes open (Lepers et al., 1997).

Biochemical markers, S-100

Given the need for supplementary diagnostic tests to aid in the identification of head injury, in recent years there have been attempts to identify simple, clinically relevant biochemical markers of cell damage to the central nervous system. This need is especially acute since the severity of head injuries cannot be determined using imaging techniques. Several proteins synthesized in astroglial cells or neurons have been proposed as such markers, but none so far has proven sufficiently useful to justify routine clinical use. Among those most commonly proposed have been CK isoenzyme BB, neuron-specific enolase, S-100 protein, glial fibrillary acidic protein, and myelin basic protein.

The S-100 protein was first described by Moore in 1965, and consists of a mixture of similar proteins composed of two immunologically distinct subunits, the α and β chains. The biologic half-life of S-100 has not been exactly established. Although originally thought to be approximately two hours, recent studies show it may be well below 60 minutes.

Wiesmann et al.(1998) determined the concentration of S-100 in blood in 200 healthy blood donors between 18 and 65 years of age. The median plasma concentration of S-100β was 0.05 ug/L, and no differences were noted for men vs. women. With increasing age, plasma concentrations decreased slightly. Serum S-100 levels >-0.2 ug/ L are considered pathologic. In MTBI, a serum level below 0.2 ug/L at admission within the first few hours post-injury predicts normal intracranial findings on CT scan.

In a pilot study of 50 patients with MTBI and normal CT scan results, Ingebretsen at al. (1999) found that 20% had detectable serum levels. Moreover, such levels were associated with an increased incidence of post-concussion syndrome and impaired neuropsychological function. In a subsequent study of another 50 patients with normal CT scans, S-100β was measured hourly for 12 hours post-injury and serum levels correlated to MRI and neuropsychological examinations one day and three months after injury. Detectable serum levels were noted in 28%, and levels were highest immediately after trauma, declining each hour after. By 6 hours post-injury, the serum level was below detectable levels for 36% of those with initially detectable levels. Also, in patients with detectable levels, a trend was noted toward impaired neuropsychological functioning on measures of attention, memory, and speed of information processing.

Although S-100β was initially considered to be unique to the nervous system, it is now apparent that it is present in other tissues as well, primarily adipocytes and chondrocytes. Concentrations in these cells however, are quite low compared with that in glial and Schwann cells. S-100β appears in serum immediately after a TBI and is rapidly eliminated. Several studies have documented the fact that S-100β levels do not vary significantly by age and gender.

Recent literature indicates that S-100β may not be a specific marker for brain injury as it has also been found to be increased in patients without brain injury (Anderson et al., 2001; deBoussard et al., 2004; Stalnacke et al., 2005; Stapert et al., 2005; Korfias et al., 2006).. Anderson reported the S-100β was highest in those with bone fractures, followed by thoracic contusions without fractures (Anderson et al, 2001). Serum S100β must be assessed carefully especially in patients with mild and moderate TBI with extra cranial trauma, in which both brain-origin and extra-cranial origin S-100β protein levels increase overall measured levels. This is of particular importance in the study of MTBI populations, as extra-cranial injuries are common, particularly when sustained in the context of motor vehicle accidents.

In addition several studies have indicated that S-100β has not been a significant predictor of symptoms associated with TBI nor neurocognitive performance following TBI (deBoussard et al., 2004; Stalnacke et al., 2005; Stapert et al., 2005; Bazarian, et. al. 2006; Naemi, et. al., 2006; Zahara, et. al., 2006). Stalnacke and colleagues indicated that S-100β may be more useful in predicting disability and may be useful in identifying those patients with MTBI that might benefit from rehabilitation services (Stalnacke et al., 2005). As pointed out by the authors of a review article on biomarkers, the lack of a strong association between a specific measure of MTBI and postconcussive symptoms may be due to the fact that PCS is a multifactorial entity influenced by physical, psychosocial, and behavioral factors (Alexander, 1995).

In a follow-up study of persons with MTBI compared to a normal control group and a non-TBI trauma comparison group, the investigators concluded that S100 proteins were not useful in detecting acute injuries but suggested that the S100A1B protein might be more appropriate to identify those patients likely to experience long-term symptom progression (Townend et al., 2002). From our own preliminary findings (see previous work) there is no positive association between S-100β and post concussive symptoms at 3 months. There is, however, an association between S-100β and overall injury severity score.

Other biochemical markers for TBI have also been reported in the literature and they include two monomers (S100A1B and S100BB) that comprise the S100β and Glial Fibrillary Acid Protein (GFAP) (Anderson et al., 2001; deBoussard et al., 2004; Nylen et al., 2005; Pelinka et al., 2004; Vos et al., 2004). With respect to S100A1B and S100BB, Anderson et al. (2001) found both types of monomers in trauma patients without head injuries. The A1B and BB concentration ratio varied, indicating no correlation with the type of trauma or tissue damage. In a study by deBoussard et al, (2004) the mean values of S100AB were significantly higher in patients with MTBI and in patients with mild orthopedic injuries when compared with non-injured controls (deBoussard et al., 2004). The authors also noted a significant correlation between time of injury and first blood draw and concentrations of S100BB but not S100β and S100A1B. Mean values of these biomarkers were higher in patients with radiological findings, but there was no relation

between S100β, S100A1B, S100BB concentrations and symptoms. They concluded that the S100AIB seems to be more specific for brain injury than S100β in patients with milder TBIs.

Recent reports indicate the GFAP, which is only found in glial cells of the central nervous system, may prove to be a better marker for TBI outcomes. The studies of GFAP involved only severe TBI but have shown that GFAP predicts outcome at 3-, 6-, and 12-months post trauma. In a study by Pelinka et al, (2004) it was demonstrated that GFAP was not increased in trauma patients without TBI nor was there a correlation between concentration levels and timing of samples. To our knowledge there have been no studies examining the predictive value of GFAP in MTBI patients. In light of reported discrepancies in the recent literature regarding the validity of the S-100 markers with respect to diagnosis and outcomes of MTBI and the lack of research involving GFAP in MTBI patients, it is apparent that further investigations are warranted.

Summary/ Discussion of Literature Review

- Mild traumatic brain injury is a common injury, both in the civilian and military populations.

- Symptoms following MTBI may be categorized as physical, cognitive, or emotional in nature

- Many studies of mild TBI have been conducted in young, healthy male athletes. Guidelines for post-injury care have largely centered on the presence or absence of "confusion" following the event.

- Although many descriptive studies of TBI outcomes have been conducted, documenting symptoms at various follow-up intervals, few predictive studies of PCS, utilizing standardized screening techniques, have been conducted. Other than for specific physical symptoms such as headache or history of loss of consciousness, few studies have utilized baseline post-concussive symptoms to predict long-term persistence of PCS.

- In practice management guidelines for mild TBI developed by the Eastern Association for the Surgery of Trauma, the authors state that "post-concussive symptoms include headache, dizziness, memory problems, and other symptoms that occur acutely in approximately 50% of mild TBI patients, and in 33% at 3 months from injury." Further, they state that "these symptoms *may* identify a subgroup of patients at subsequent increased risk for prolonged cognitive deficits as a result of their injury." However, no studies are cited to substantiate this theory.

- Various tests, including those for balance, serum biomarkers, and speech and neuropsychology measures, have been proposed as possible predictors for cognitive and other post-concussive symptoms.

Most studies that do follow patients for an extended time period document the symptoms associated with the head injury, sometimes comparing to a population without MTBI or a population with moderate or severe head injuries. The purpose of the current research; however,

is to compare patients to themselves, to predict which factors, measures post-injury, are useful predictors of the subgroup who go on to have persistent post-concussive symptoms

RESULTS:

Overview of Subject Recruitment and Follow-up:

Actual screening and recruitment was initiated on October 6, 2003. At the close of recruitment on September 30, 2006, 2,560 potential subjects had been screened and 180 recruited. Table 4 describes the reasons and frequencies for the 2,380 potential subjects who were not recruited. Over one-third of the potential subjects were not recruited due to additional associated injuries. These injuries included brain injury requiring medical or surgical intervention, spinal cord injury or thoracic injuries requiring intubation, and those on mechanical ventilation.

Table 4: Reasons Potential Subjects Were Not Recruited	N
Age	8
Non-local resident	34
No loss of consciousness or mental status changes	241
Mini Mental Status Score <8/10	26
Non-English speaker	96
Associated injuries (i.e., brain injury requiring intervention, thoracic injuries requiring intubation)	855
Discharged before enrollment completed	294
Refused	199
Penetrating injury	7
Other (i.e., past medical history, active military, probation/parole)	615
Readmission to the hospital	5

The overall follow-up rate is depicted in Table 5. Follow-up rates range from a high of 87% at 7-10 days post-injury to a low of 57% at 12-months post-injury. The high follow-up rate at 7-10 days may be a result of many subjects returning to the STC clinic for medical team appointments at that time and scheduling of evaluations on the same day whenever possible. The follow-up rate decreases throughout the remainder of the study, perhaps due to the fact that many subjects have returned to normal activities and are therefore not returning to the STC clinic for additional follow-up. Follow-up appointment times were made available during non-traditional hours (evenings, weekends) in an attempt to capture those subjects who were back to work and therefore unable to return for assessment during traditional weekday work hours; however, few subjects took advantage of this option, choosing instead to complete a phone interview in lieu of return visit.

Table 5: Follow-up Status of the 180 Enrolled Subjects*

Evaluation	Completed N	Eligible N	Follow-up Rate %
3-5 day	138	180	77
7-10 day	157	180	87
3 month	110	180	61
6 month	102	173	59
12 month	81	142	57

*An evaluation is considered complete if the interview and the symptom checklist were completed.

The details of follow-up status are described in Table 6. Telephone follow-ups occurred at a much higher rate during the acute phase of recovery as opposed to later in recovery (37% at 3-5 days versus 12% at 12-months post-injury). When subjects were unable to complete the entire battery of tests, priority was given to those components completed at previous visits. Ten subjects were withdrawn from the study (9 withdrew consent and for one subject, a neurosurgical intervention, was initiated after consent was obtained).

Table 6: Detailed Description of Follow-up Status of the 180 Enrolled Subjects

	Complete*	Partial**	Telephone	DNKA***/ Cancels	Withdrawn	Lost to F/U****	Eligible
	N	N	N	N	N	N	N
Initial	14	166					180
3-5 day	9	62	67	21	1	20	180
7-10 day	29	62	66	9	3	11	180
3 month	35	39	36	13	3	54	180
6 month	48	20	33	5	9	58	173
12 month	47	17	17	4	10	47	142

*Complete=all evaluation components assessed
** Partial= one or more evaluation components not assessed
*** DNKA= did not keep appointment
**** F/U= follow-up

Demographic Characteristics:

A total of 180 patients were enrolled into the study. Since they were admitted to a trauma center, many also had other injuries; approximately one third had lower extremity injuries in addition to the mild TBI. Characteristics of the study population are shown in Table 7.

Table 7: Baseline Demographic Characteristics of Subjects
N=180

- Demographics
  - Mean age 35 years
  - 64% Male
  - 47% ≤ High School Education
  - 79% Employed Full or Part-time
  - 66% Single
  - 88% Lived with others
  - 55% Motor Vehicle Collision
- Medical History
  - 22% Previous Mild TBI
  - 22% Lifetime Alcohol Dependence
  - 22% Depression
- Injury Characteristics
  - 70% Injury Severity Score ≥ 9
  - 81% Glasgow Coma Score = 15
  - 59% Associated Extracranial Injuries

Analysis of Selection Bias:

Baseline characteristics were compared for those subjects who did and did not complete the 3-, 6- and 12-month follow-up evaluations. Table 8 lists characteristics of subjects who were significantly less likely to be followed. In addition, at 6-months, subjects who were not followed were significantly younger than those who completed the follow-up evaluations (33 vs. 36 years of age, p-value=0.04).

Table 8: Significant Differences in Follow-up Rates

3-month		**6-month**		**12-month**	
	p-value		p-value		p-value
Single (56%) Married (71%)	0.05	≤ High school Yes (46 %) No (66 %)	0.007	Depressive symptoms pre-injury Yes (30%) No (49 %)	0.03
≤ High school Yes (49%) No (72%)	0.003			Previous mild TBI Yes (31 %) No (49%)	0.05
Unemployed (37%) Employed (4%)	0.03			Lifetime alcohol dependence Yes (28%) No (50%)	0.02

Data Analyses:

The purpose of these analyses was to describe the natural history of mild TBI in this population of trauma patients, with a focus on the initial symptoms, and presence of persistent symptoms at the various follow-up contacts. Symptoms have been described in several ways, including: (1) the number of symptoms, (2) the presence of four or more symptoms, and (3) the severity of symptoms. Severity was estimated by multiplying the severity (on a scale of 1 to 10) of each individual symptom, as described by the patient, and then multiplying the severity by the number of days the symptom was experienced.

Post-concussive syndrome (PCS) was defined, for the purpose of these analyses, as the presence of four or more symptoms post-injury. Other analyses are based on the findings from the Well-Being Score, and a return to work variable. Symptoms were utilized as both risk factors (i.e., predictor variables) and outcome variables, as in the instance of PCS, which is defined as the presence of the number of symptoms, in this case, four or more. For example, a question of interest might be whether subjects who experienced headache in the week following their injury were more likely to experience PCS at 3 months post-injury. In addition to individual symptoms as predictor variables, symptoms have been grouped as to whether they were physical, emotional, or cognitive in nature, in order to determine which types of symptoms are most associated with the subsequent risk of PCS.

Description of Baseline Test / Interview Data:

The Concussion Symptom Checklist. As previously describe, the checklist consists of answers to questions regarding twelve concussion-related symptoms, including questions related to 6 physical, 3 emotional, and 3 cognitive domains. Each question addresses symptoms experienced during the past week, including the number of days involved and the severity of the symptom, on a scale from 1-10.

Magnitude of Symptoms - frequency of the symptom multiplied by the intensity of symptom (range from 0 {not having symptom} to 70 {having symptom everyday with and intensity of 10})

Severity of Symptoms - sum of all symptoms magnitude (range 0 to 840)

Demographic Variables. For the purpose of the analyses, age was grouped into tertiles; 18 to 25 26-40 and 41-64 years old.

Education. Education was divided into two groups, with those subjects with less than high school education or graduated from high school versus those who graduated from high school and had advance education.

Injury Mechanism. Many of the subjects in the study were involved in motor vehicle-related collisions. For the purpose of the analyses, those in motor vehicle-related incidents (i.e., passenger vehicle, motorcycle/dirtbike, and atv) were contrasted with all other subjects.

***Lifetime Alcohol Dependence*.** Lifetime alcohol dependence was ascertained based on answers to the four questions from the CAGE questionnaire. A score of two or more was defined as lifetime dependence.

Extracranial Injury (i.e. presence of other injuries). Extracranial injury was defined as presence of an injury to any one or more of the following: thoracic organ or skeleton, abdominal organ, lower extremity skeleton, or pelvic fracture or dislocation.

Simple Reaction Time Thruput (SRT). – SRT is the number of correct responses per minute of time available while responding to an asterisk appearing on the monitor.

Recall. Recall is a testlet from SCATBI that evaluates of various types of memory including semantic memory, episodic memory, immediate recall, delayed recall, recall with interference and long-term memory

History of Depression. History of depression was from the initial interview. It was defined by, a positive response to either of the following statements: During the past month, have you been bothered by 1) feeling down depressed or hopeless or 2) little interest or pleasure in doing things

Balance Testing. Not all subjects were able to be balance tested, primarily due to other injuries, especially lower extremity injuries. Eighteen subjects were tested at either the initial or 3-5 day visits, with an additional 23 at the 7-10 day visit. At the various follow-up visits, more subjects were able to be tested. Sixteen subjects had at least one of the baseline, 3-5 day or 7-10 day balance tests conducted, as well as all three of the longer-term follow-up visits. Most subjects who were tested using the Neurocom Balance were also able to perform the BESS balance test. From this testing, the following measures were derived: the total composite score (from the NBM), the individual error scores (firm and foam) and total error scores, from the BESS.

An increasing number of errors while using the BESS firm test (i.e. feet placed on the floor) was highly correlated with a lower composite score (i.e., poor balance) at the initial post-injury visit ($r=-0.46$) and at the 3-5 day visit ($r=-0.65$). Among the balance tests, only the number of errors made while taking the BESS test on a firm surface was associated with increasing symptom severity at 3 months ($r=0.47$), 6 months ($r=0.35$), and 12 months ($r=0.47$).

Tables 9 to 12, in Appendix D, show the comparison of mean balance data derived from the earliest visit (initial assessment, 3-5 or 7-10 days post-injury) (for both NBM and BESS) for physical, emotional, and cognitive symptoms as well as PCS at the 3 month, 6 month, and one year follow-up intervals. As shown in Table 9, physical symptoms were significantly correlated with both the BESS firm and total error scores at 6 months. That is, those with higher error scores within the first 10 days post-injury had significantly more physical symptoms 6 months post-injury.

The BESS firm error scores were also significant predictors of emotional symptoms at the 3 month follow-up (Table 10). No associations between early balance tests and cognitive symptoms were noted, however (Table 11). Finally, the BESS firm error scores were significant

predictors of PCS at 3 months; those with more errors were significantly more likely to have four or more symptoms at the 3 month visit (Table 12).

S-100 Blood Biomarker. Blood samples were obtained on 168 of the 180 subjects. Eighteen were eliminated from the analysis because the testing was carried out 6 hours or more after the injury, resulting in available levels for 150 subjects. The results ranged from .005 ng/ml (undetectable) to .565 ng/ml. One third of the results were recorded as undetectable, and were thus eliminated from further analyses. Only 17 of the test results were higher than .200 ng/ml, a result cited in the literature as suggestive of pathology.

Preliminary analyses showed an inverse relationship between S-100β levels and number of symptoms reported post-injury (at 3, 6, and 12 months), an unexpected finding. At each of these time intervals there was an inverse association between S-100β levels and either number of symptoms or symptom severity. Given reports in the literature on the association between S-100β and extracranial injuries, further analyses were conducted. The results confirmed the fact that S-100β levels were significantly higher among those patients with thoracic, abdominal, spine (cord or vertebrae), and extremity injuries, especially lower extremity fractures.

Receiver operating characteristic (ROC) curves were computed to determine whether S100B does a better job of predicting outcome than chance alone. An ROC curve is a graphical representation that describes the trade–off between false positive and false negative rates at various cut-off points. An area under the curve (AUC) of 50%, following the diagonal, indicates no more than random agreement between S100B and outcome. Our data indicate that S100B does not predict (a) 4 or more symptoms or (b) inability to return to work, as evidenced by AUC readings hovering around 50%. As indicated above, our data suggest that S100B is associated with injury; the AUC indicates that, 75% of the time, S100B test results will distinguish between extracranial and non-extracranial injuries. S100B is also somewhat associated with the presence of emotional symptoms (AUC = 57%). See Figures 1 to 6 in Appendix D.

S100B protein levels have been linked to disability and low levels of life satisfaction after mild TBI (Stalnacke et al., 2005). The Word Memory Test (WMT) is a test of effort and motivation that is viewed as more sensitive to levels of effort than to brain injury (Green et al, 2001). We assessed the relationship between S100B and effort, as measured by the WMT, in our sample of subjects with mild TBI. Subjects were evaluated at 7-10 days (N=46) and 3 months (N=41) post injury. As expected, results of analyses indicated no relationship between S100B protein levels and performance on the WMT (both immediate recall and delayed recall trials) at either time point. This provides evidence that effort is not an issue in this MTBI population.

SCATBI. The SCATBI is divided into several sections designed to capture various aspects of cognition, including recall, reasoning, organization, orientation, and higher function (recall and reasoning). Using the data from the initial encounter, only the recall portion of the test was noted to be significant, predicting the number of symptoms at 3 months. That is, the lower the successful recall scores, the more symptoms experienced by the subject 3 months post-injury. For this reason, recall was the subtest selected for inclusion in later regression analyses.

ANAM. From the ANAM tests, the simple reaction time throughput measure (a measure of the number of correct responses per time interval) was chosen based on consultation with our neuropsychology staff members. It was analyzed as a continuous variable and, subsequently, as a categorical variable based on tertiles.

The General Well-Being Schedule. This scale reflects both positive and negative feelings, and covers six dimensions including anxiety, depression, general health, positive well-being, self control, and vitality. Variable clustering correlation methods were used to determine which dimensions of well-being should be included in the analysis. It was determined that the total well-being score ascertained from all six dimensions of well-being was the appropriate measure to use.

Data Analyses:
The purpose of the analyses presented below is twofold:

(1) To describe the natural history of mild TBI, and the prevalence of various post-concussion symptoms over time, and

(2) To identify factors which, based on initial post-injury assessments, best predict the subset of persons with mild TBI who have persistent, long-term symptomatology.

Descriptive Analyses

Using the Concussion Symptom Checklist, individual symptoms usually associated with mild traumatic brain injury were assessed at each of the follow-up visits. Since the Checklist inquires about symptoms experienced by the patient in the past week, data obtained at the initial enrollment visit refer to pre-injury symptomatology. Twelve symptoms were assessed, addressing the following **physical** (headache, dizziness, blurry/double vision, fatigue, sensitivity to light, and sensitivity to noise), **cognitive** (difficulty concentrating, memory problems, and trouble thinking) and **emotional** (anxiety, depression, and irritability) domains.

Figure 7 shows the change in symptoms, over time, for physical, cognitive, and emotional symptoms. Table 13 shows the changes in prevalence for each of the individual symptoms. It is apparent that physical symptoms were the most prevalent, both before the injury as well as post-injury. The symptom with the highest prevalence in the week prior to injury was fatigue (56.1%), followed by headache (36.7%), and irritability (31.7%).

Over time most of the physical symptoms (headache, sensitivity to light or noise, blurry or double vision) increased at the 3-10 day follow-up visit, then gradually returned to baseline levels by the 3 or 6 month follow-up assessments. Dizziness, however, although declining considerably at 3 months, remained considerably higher than pre-injury levels even at one year post-injury.

Table 13: Prevalence of Symptoms by Follow-up Visit

	Pre-Injury N=180		3-10 Day N=164		3 Month N=110		6 Month N=102		12 Month N=81	
	n	%	n	%	n	%	n	%	n	%
Physical										
Headache	66	36.7	117	71.3	53	48.2	41	40.2	33	40.7
Dizziness	14	7.8	113	68.9	20	18.2	17	16.7	19	23.5
Blurry/Double Vision	14	7.8	50	30.5	15	13.6	7	6.9	12	14.8
Fatigue	101	56.1	152	92.7	54	49.1	50	49.0	46	56.8
Sensitive to light	36	20.0	60	36.6	20	18.2	20	19.6	13	16.1
Sensitive to noise	18	10.0	44	26.8	16	14.6	12	11.8	8	9.9
Cognitive										
Concentration	30	16.7	100	61.0	39	35.5	34	33.3	24	29.6
Memory	41	22.8	85	51.8	49	44.6	38	37.3	31	38.3
Trouble Thinking	11	6.1	50	30.5	20	18.2	17	16.7	10	12.4
Emotional										
Anxiety	37	20.6	81	49.4	30	27.3	28	27.5	23	28.4
Depression	26	14.4	63	38.4	29	26.4	27	26.5	17	21.0
Irritability	57	31.7	104	63.4	47	42.7	43	42.2	30	37.0

With respect to cognitive symptoms, 16.7% of subjects at the initial visit complained of difficulty concentrating prior to injury. This symptom peaked at the 3-10 day visit, then declined at three months, but remained at levels approximately twice the pre-injury level at 6 and 12 month follow-up intervals. A small proportion (6.1%) of subjects reported "trouble thinking" prior to injury, and the prevalence increased to 30.5% at 3-10 days. Again, while declining at the 3-month visit, trouble thinking also persisted and was reported by 16.7% and 12.4% of subjects at 6 and 12 months, respectively. With respect to memory problems, the prevalence was 22.8% pre-injury, increasing dramatically to 51.8% at the 3-10 day visit. While memory problems declined slightly at 3 months, they remained above normal through the one-year follow-up, with 38.3% reporting such problems at that time.

With regard to emotional symptoms, 20.6% of subjects reported anxiety in the week prior to injury. By the 3-10 day visits, approximately half of the cohort reported such symptoms; by 3 months the prevalence of anxiety had declined somewhat, but remained above baseline levels, with 28.4% reporting this problem one year post-injury. The prevalence of reported depression was 14.4% prior to injury, again peaking at the 3-10 day period and declining to 21.0% at the one year follow-up. Irritability, on the other hand, while reported by almost one third of subjects at their initial visit, declined by 3 months and was back to pre-injury levels by 6 and 12 months.

Figure 7: Prevalence of Physical, Cognitive and Emotional Symptoms by Follow-up Visit

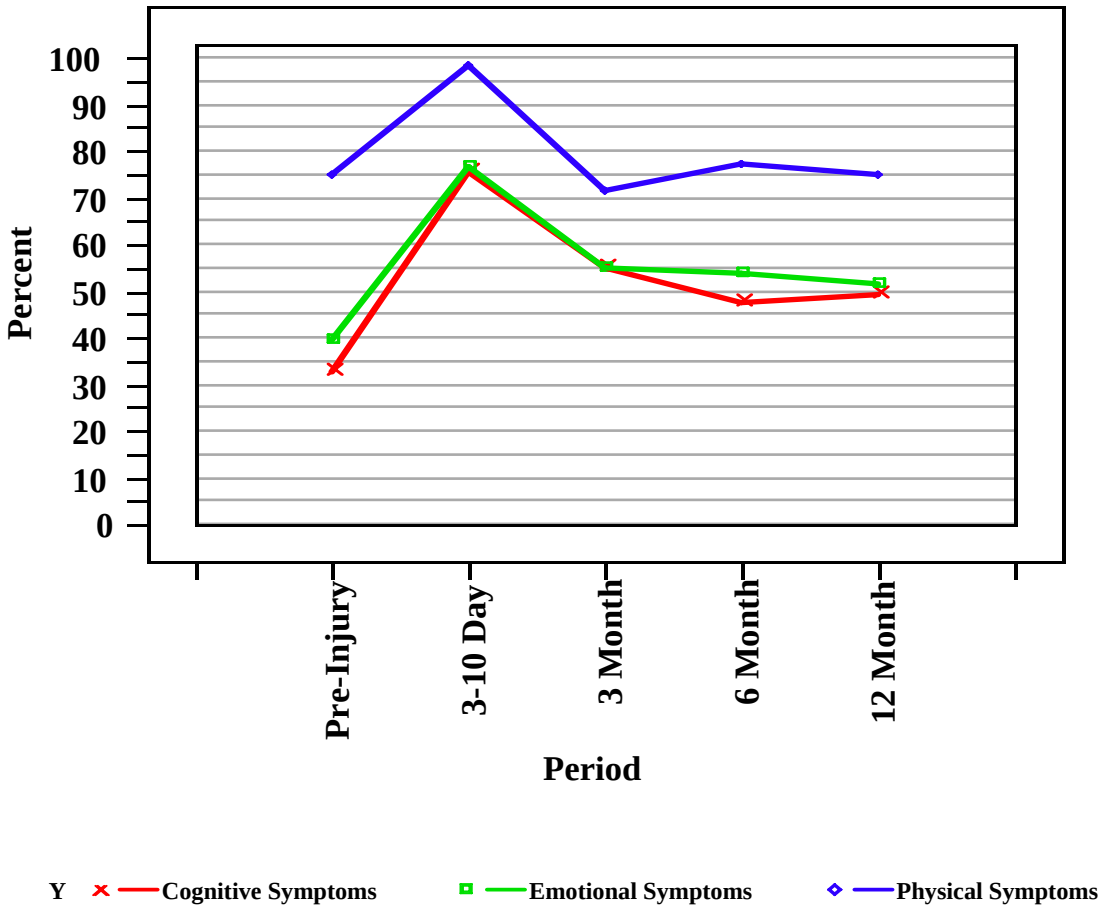
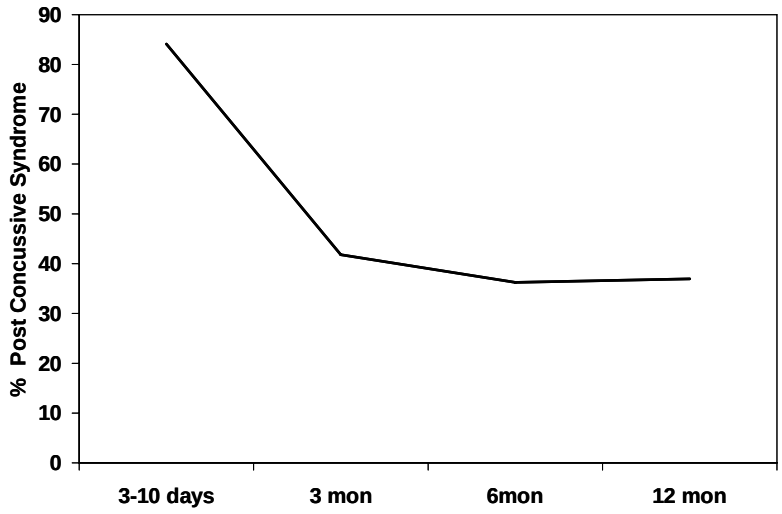


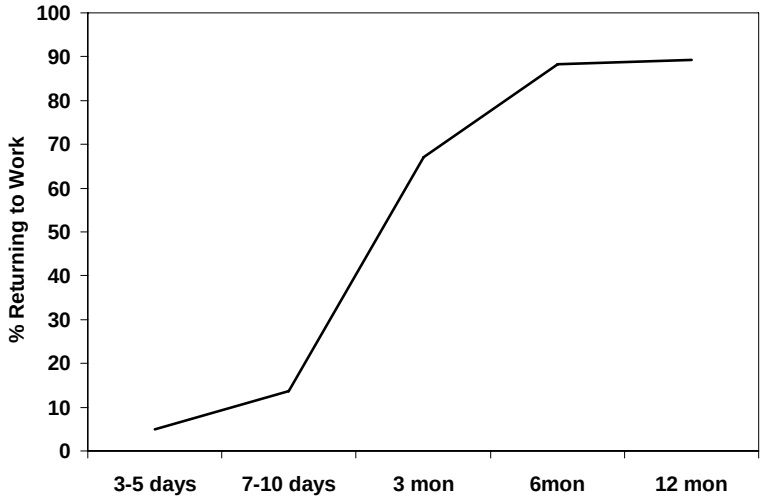
Figure 8 shows the proportion of subjects with PCS at each of the various follow-up intervals. Even at the 6 and 12 month post-injury periods, it is apparent that more than one third (37%) of participant still experienced post concussive syndrome.

Figure 8: Prevalence of Post Concussive Syndrome by Follow-up Visit



As shown in Figure 9, of those subjects who were either employed or in school before their injury, the majority ultimately returned to their pre-injury capacity. However, at 7-10 days post-injury, only 13.7% were back to work/ school. By three months, two thirds had returned. At six months post-injury almost all of those who ultimately returned to work/ school had already done so, with a rate of employment/ school attendance of 88.2% at 6 months and 89.3% at one year. In the analytic findings described later, the characteristics of those who did and did not return to work are identified.

Figure 9: Percent Returning to Work or School
Among Subjects Employed or in School Immediately Before Injury
(N = 161)



In summary, it is evident that most physical symptoms peaked during the 10 day period following the injury and then returned approximately to baseline levels by the 3-month visit. In contrast, the majority of cognitive and emotional symptoms had a lower prevalence pre- injury, but was more likely to increase over time and, for the most part, did not return to baseline levels, even one year later.

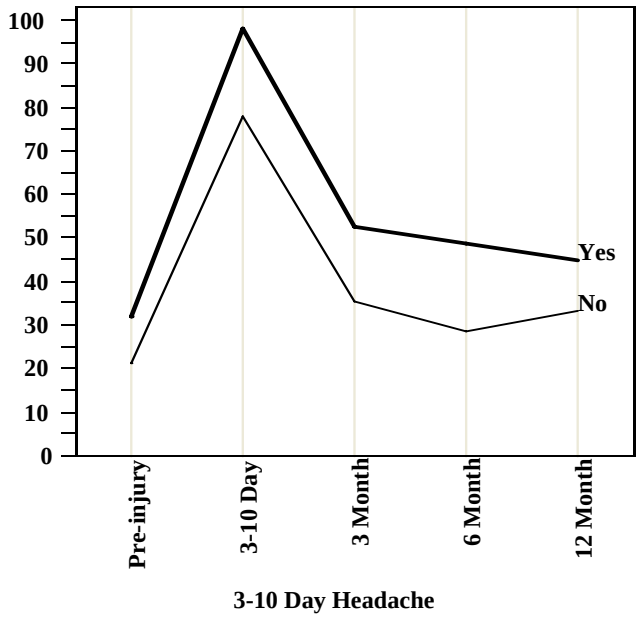
Persistence of 4 or More Symptoms (Post-Concussive Syndrome)

As mentioned previously, post-concussive syndrome is defined as the presence of four or more symptoms. The incidence of PCS at each follow-up visit was examined among those with the presence or absence of each individual symptom at 3-10 days post-injury. Figure 10 presents the data for those subjects with and without headache at 3-10 days post-injury. It shows that subjects suffering from a headache immediately following injury were more likely to develop PCS than were study participants who did not report having a headache during the 3 to 10 day follow-up period.

Findings regarding each of the remaining symptoms may be found in Appendix D, Figures 11-21. With the exception of dizziness, study participants reporting a specific symptom at 3-10

days post-injury were more likely to report 4 or more symptoms at each follow-up visits as compared to those not reporting the symptom. However, the spread between the "yes" and "no" lines varies from symptom to symptom, with some, like memory, converging again over time. For other symptoms, such as anxiety, it is apparent that the discrepancy between the yes and no symptom lines even increases between the 3 and 6 month follow-up periods. That is, it is apparent that subjects experiencing anxiety in the week to 10 days following their injury had a much higher incidence of PCS at subsequent follow-up intervals. The significance and relative predictive value of these symptoms will be described further under the section on Analytic Findings.

Figure 10: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Headache At 3-10 Days Post-Injury



II. Analytic Findings.

The purpose of this part of the study was to identify factors, (including demographic factors, 3-10 day post-injury symptoms , balance test findings, S-100 results, and speech and neuropsychological test results) that best predicted PCS at the 3 month, 6 month, and one year follow-up intervals for this population.

Results are presented as univariate associations between each of the previously mentioned tests. Univariate findings were based on regression models, with the outcome as one of the following: number of symptoms, severity of symptoms, four or more symptoms (PCS), lack of well-being, and inability to return to work.

From those analyses, the variables found to be associated with PCS were then included in multiple regression analyses, in order to determine the relative importance of each factor and the

statistical significance of the findings. Multiple logistic regression models are presented for two of the outcomes (four or more symptoms and inability to return to work) at each of the follow-up intervals (3, 6, and 12 months post-injury). Since not all tests were performed on each subject, and not all subjects were able to return repeatedly for testing, the number of cases in the various regression models varies (because cases with incomplete data are dropped from the model). Thus, in general, the univariate findings are based on larger numbers of cases.

A. Univariate Predictors of Outcomes

Each of the baseline factors was examined independently, in order to determine whether it was useful to predict post-concussive symptoms at future time intervals, namely at 3, 6, and 12 months post-injury. Post-concussive symptoms were examined in several ways, including the number of symptoms, the severity of the symptoms, and the presence of four or more symptoms (PCS). Other regression outcomes examined were the lack of total well being and the inability to return to work.

Findings from these univariate analyses are summarized in Tables 10-12 and can be found in Appendix D. Estimates (or odds ratios) and p values from the regression analyses are presented for the three, six, and twelve month follow-up intervals, respectively.

1. Three month follow-up findings (Table 14):

Age. Age alone was not found to be predictive of symptomatology, lack of well being or inability to return to work at 3 months post-injury

Gender. Women, as compared to men, had significantly more symptoms, more serious symptoms, and lower well being scores at 3 months post-injury. Also, women were significantly more likely to report four or more symptoms at 3 months post-injury, but no differences in return to work by gender were noted.

Education. Those with a high school education or lower reported significantly more symptoms and more severe symptoms at 3 months. However, no differences in well-being or the ability to return to work were noted by education. Also, those with less education were twice as likely to experience four or more symptoms at 3 months, a difference that was of borderline statistical significance.

Injury Mechanism. For the purpose of this analysis, subjects were divided into two groups: those with and without injuries resulting from vehicular crashes. No differences were noted between the two groups with regard to subsequent symptomatology or well-being. No differences were noted between subjects injured in motor vehicle crashes vs. other mechanisms, with regard to PCS or the inability to return to work at 3 months.

Pre-injury Depression. Subjects reporting a history of depression were significantly more likely to have more symptoms, more severe symptoms, and lower well being at 3 months. Those subjects who reported a history of depression were significantly more likely to experience PCS

(four or more symptoms at 3 months post-injury), and were also significantly less likely to have returned to work at that time.

Previous Brain Injury. Subjects who reported having had a previous brain injury reported significantly *fewer* symptoms at 3 months. However, no differences were noted with regard to symptom severity or well being. Since there were only 39 cases who reported a previous mild head injury, this variable was not included in the subsequent regression models.

Lifetime Alcohol Dependence. Subjects determined to have lifetime alcohol dependence did not differ from those without dependence, with respect to reported symptomatology or well being at 3 months.

Presence of Other Injuries. At 3 months, neither symptomatology (number of symptoms, PCS, or severity of symptoms) nor the inability to return to work were associated with the presence of extracranial injuries.

S-100. The S-100β data were not found to predict symptoms (number, severity, PCS or total well-being at 3 months**.** However, the association with return to work/school showed a borderline significance; that is, those with lower levels were more likely to return to work 3 months following their injury.

Simple Reaction Time Thruput. This test was administered using the ARES at the initial screening visit and the ANAM at the 7-10 day follow-up. However, data from neither of these time intervals were useful in predicting the number of symptoms, the symptom severity, the prevalence of 4 or more symptoms, total well being or return to work at three months post-injury.

Scales for Cognitive Assessment of TBI (SCATBI). None of the SCATBI measures, obtained at the initial encounter or 7-10 day visit, were predictive of symptoms or well-being at 3 months post-injury or the presence of four or more symptoms or return to work at 3 months.

Balance Tests. As described in the Methods section, two types of balance testing were conducted: the NBM test, which generated a composite score, and the BESS, which consisted of total error points from the testing conducted on the foam, the floor, and the sum of both. The BESS error points "firm", which refers to the testing conducted with the patient standing on the floor, was a significant predictor of the number of symptoms, severity of symptoms and PCS at 3 months, as well as the total well being; it was not related to return to work, however. In addition, the composite score exhibited borderline significance with respect to the prediction of total well-being. While the composite score from the NBM showed borderline significance with respect to predicting PCS at 3 months, both the "error points firm" and total error points from the BESS data were significant risk factors for PCS at 3 months.

Symptoms. As previously described, symptom measures were obtained at the enrollment visit for a history of the patient's symptoms the week preceding the injury. Symptom checklists were then again administered at 3-5 and 7-10 day visits, which were combined for analysis purposes (since not all subjects returned for both visits) and at subsequent follow-up visits. Symptoms

were analyzed according to individual symptoms or grouped according to whether the symptoms were physical, emotional, or cognitive in nature.

Pre-injury Symptoms. Pre-injury symptomatology noted to be useful for the prediction of the number of post-concussive symptoms reported at 3 months included physical and emotional, *but not cognitive*, symptoms. In particular, headache, anxiety, depression, and light and noise sensitivity were significant predictors of the number of symptoms experienced at 3 months post-injury. Similar findings were noted with respect to predictors for PCS (except for headache) and symptom severity, with the exception that pre-injury fatigue was also significant, while sensitivity to noise was not.

However, findings were slightly different in the univariate analysis of pre-injury symptoms with respect to the inability to return to work by 3 months. Subjects experiencing emotional and cognitive symptoms, *but not physical symptoms*, were at higher risk of not returning to work. Among the individual symptoms, only pre-injury depression or memory problems were noted to be significant predictors of an inability to return to work.

Post-injury Symptoms. For symptoms reported 3-10 days post-injury , those that were significantly associated with the number of symptoms at 3-months included emotional and cognitive symptoms, *but not physical.* Thus, the findings based on post-concussive symptoms differ somewhat from those reported above for pre-injury symptoms. Included among this list of symptoms are: headache, anxiety, depression, difficulty concentrating, memory, vision, trouble thinking irritability, and light and noise sensitivity. Similar predictors for severity of symptoms at 3 months were noted, with the exception of dizziness, which was also associated with symptom severity.

On the other hand, every subject experiencing physical symptoms at 3-10 days post-injury reported four or more symptoms at 3 months. Other predictors of PCS that occurred within 3 to 10 days following injury included the presence of emotional symptoms, anxiety, depression, memory problems, trouble thinking, irritability, and light and noise sensitivity. Patients who reported emotional symptoms following their head injury were eight times more likely to experience PCS at 3 months, as compared to those who did not report such symptoms following their injury.

Patients who were significantly less likely to have returned to work by 3 months reported post-injury symptoms that included the presence of emotional symptoms, anxiety, depression, problems with concentration, dizziness, memory, difficulty thinking, irritability, and noise sensitivity. Every subject experiencing fatigue or the presence of physical symptoms at 3-10 days post-injury were unable to return to school or employment by 3 months.

2. Six Month Follow-up Findings (Table 15):

Findings from univariate regression models for a comparison of baseline testing with six month outcomes revealed the following findings:

Age. Age was not a significant predictor of the number of symptoms, severity of symptoms, presence of 4 or more symptoms, well being, or the ability to return to work at six months post-injury.

Gender. At six months, women with mild TBI experienced more symptoms, more severe symptoms, and decreased well being, as compared to men. Women were also significantly more likely to experience four or more symptoms at the 6 month follow-up; however, no differences were noted, by gender, with respect to return to work.

Education. Level of education was not found to be a useful predictor of symptomatology, well-being, or return to work at six months.

Injury Mechanism. No differences were noted between those subjects injured in motor vehicle crashes, as opposed to other injury mechanisms, with respect to outcomes at 6 months.

Pre-injury Depression. Although pre-injury depression was not a significant predictor of number of symptoms or severity of symptoms at 6 months, it was a significant predictor of decreased well being.

Lifetime Alcohol Dependence. A history of lifetime alcohol dependence was not associated with symptomatology or well-being at 6 months.

Presence of Other Injuries. At 6 months, symptomatology (number of symptoms, 4 or more symptoms, or severity of symptoms), total well being and the inability to return to work were not associated with the presence of extracranial injuries.

S-100. The S-100β data were not found to predict symptoms (number, severity, or ≥4 symptoms), total well-being or return to work at 6 months.

Simple Reaction Time Thruput. The simple reaction time was not a useful predictor of six month symptomatology, well being, or return to work, either for the initial encounter or the 7-10 day visit.

SCATBI. None of the SCATBI subtests were associated with symptoms (number, severity, or ≥4 symptoms), total well being or the ability to return to work at six months.

Balance: None of the balance tests conducted with in the first 7-10 days predicted symptomatology, well being, or the ability to return to work at 6 months; however the BESS error points "firm" demonstrated a borderline significant association with severity of symptoms at 6 months.

Symptoms. Symptoms reported either at baseline or within 3-10 days post-injury were examined to determine which ones were significant predictors of symptoms and/or well-being six months post-injury.

Pre-injury symptoms. In general, all three types of pre-injury symptoms (i.e., physical, cognitive, and emotional) were significant predictors of the number of symptoms experienced six months later. For symptom severity and well-being, however, only the emotional and cognitive symptoms were significant.

With respect to specific pre-injury symptoms, headache, anxiety, depression, concentration, irritability and sensitivity to noise were significant risk factors. Similar findings were noted for symptom severity, except dizziness was also significant, whereas noise sensitivity was not. Predictors of decreased well-being at 6 months include: headache, anxiety, depression, concentration, and noise sensitivity.

For pre-injury symptoms, all types (i.e., physical, cognitive, and emotional) were significant predictors of post concussive syndrome (4 or more symptoms) at the 6 month follow-up. Those symptoms with specific prognostic power included: headache, anxiety, depression, concentration difficulties, and irritability. None of the reported pre-injury symptoms, however, were associated with return to work at 6 months.

Post-injury symptoms. For symptoms reported at 3-10 days post-injury, emotional and cognitive symptoms were noted to be significant predictors of number and severity of symptoms at 6 months. Emotional symptoms were also significant predictors of decreased well-being.

Specific symptoms that were risk factors for greater numbers of symptoms at 6 months include: anxiety, concentration, memory, vision, thinking, irritability, and light and noise sensitivity. Similar predictors were noted with respect to symptom severity, but depression was also significant. Symptoms found to be significant predictors of decreased well-being included anxiety and depression, memory, difficulty thinking, and noise sensitivity. With respect to return to work at 6 months, trouble thinking was a significant predictor of inability to resume previous activities; anxiety also showed borderline significance.

For symptoms experienced at 3-10 days post-injury, emotional and cognitive symptomatology was significantly associated with PCS at 6 months. Specifically, the symptoms identified as predictors of PCS were: anxiety, depression, concentration, vision, trouble thinking, irritability, and light sensitivity. Noise sensitivity showed borderline statistical significance. Trouble thinking was a significant predictor of inability to return to work at 6 months; anxiety also showed borderline significance.

3. Twelve Month Follow-up Findings (Table 16):

Age. Age was not a significant predictor symptoms or well-being at 12 months post-injury. There was a borderline association with return to work.

Gender. Women had significantly more symptomatology and decreased well-being at the one year follow-up. There was no association with the in ability to return to work at one-year post-injury.

Education. As was the case for the three and six month follow-ups, educational level did not predict subsequent symptomatology, well-being, or return to work at 12 months post-injury.

Injury Mechanism. No association was noted between injury mechanism and subsequent symptomatology, well being, or return to work at 12 months post-injury.

Pre-injury Depression. As with the predictors for the six month data, a history of depression was not a significant predictor of number, severity or presence of four or more symptoms, but it was a significant risk factor for decreased well being and the inability to return to work at one year.

Alcohol Dependence. Lifetime alcohol dependence was not noted to be associated with either symptomatology, well-being, or return to work at one year.

Presence of Other Injuries. At one year post-injury, symptomatology (number of symptoms, 4 or more symptoms, or severity of symptoms), total well being and the inability to return to work were not associated with the presence of extracranial injuries.

S-100. The S-100β data obtained on admission were not found to predict symptoms (number, severity, or ≥4 symptoms), total well-being or return to work at 12 months post-injury.

Simple Reaction Time Thruput. The simple reaction time obtained at the initial encounter was not a useful predictor of 12 month symptomatology, well being, or return to work. The inability to return to work at 12 months was predicted by the 7-10 day simple reaction time; however four or more symptoms were not predicted. Participants with slower reaction times at 7-10 days post-injury were less likely to return to work by one year as compared to those with faster reaction times.

SCATBI. Recall at the initial encounter was found to be associated with the number of symptoms and severity of symptoms at one year post-injury. Higher functioning scores, of which recall is part, were also associated with decreased number and severity of symptoms at 12 months. Four or more symptoms, well being and return to work were not predicted by initial SCATBI scores. Of the SCATBI scores obtained at 7-10 days post injury, organization was associated with return to work and orientation was associated with both number of symptoms and well being at 12 months post-injury.

Balance: None of the balance tests conducted within the first 7-10 days predicted symptomatology, well-being, or the ability to return to work at 12 months.

Symptoms*:*

Pre-injury Symptoms. Similar to the findings from the previous follow-up intervals, all three types of pre-injury symptoms (physical, emotional, and cognitive) were important predictors of both number of symptoms and symptom severity at 1 year. In addition, specific pre-injury symptoms associated with the number of symptoms at 1 year were exactly the same as those related to symptom severity: headache, anxiety, concentration, irritability and fatigue. Fewer specific pre-injury symptoms were associated with PCS at one year, however. These factors included headache, anxiety, irritability, and the presence of emotional symptoms.

Anxiety and depression and the presence of emotional or cognitive symptoms were significant predictors of decreased well-being at the 1 year mark.

All subjects who experienced dizziness or vision problems before their injury had occurred were unable to return to work by 12 months. Other pre-injury risk factors for this outcome included anxiety and difficulty concentrating.

Post-injury Symptoms. With regard to symptoms reported post-injury (at 3-10 days), only emotional and cognitive symptoms were found to be predictive. Symptoms noted to be significant predictors of post-concussive symptoms at one year include anxiety, concentration, difficulty thinking, irritability, and light and/or noise sensitivity. For symptom severity, significant predictors were anxiety, depression, memory problems, difficulty thinking, irritability, and light sensitivity. Decreased well-being was associated with anxiety, memory and thinking problems, and noise sensitivity.

Those reporting headache, anxiety, difficulty thinking, irritability and noise sensitivity at the 3-10 day visit had a significantly higher incidence of PCS at one year. All subjects experiencing physical or emotional symptoms by 3 to 10 days following injury reported 4 or more symptoms at 12 months. Factors related to an inability to return to work included problems with memory at 3-10 days post-injury. In addition, each person who did not return to work suffered from fatigue and at least one emotional or cognitive symptom at the 3-10 day visit.

B. Regression Models

1. To Predict Post-Concussive Syndrome

Based on the previous analyses, it was apparent that there were distinct differences in the predictive value of specific subgroups of physical symptoms. That is, although there was a high prevalence of the three symptoms of headache, dizziness, and fatigue, these symptoms did not predict the subsequent persistence of post-concussion syndrome. The remaining three symptoms (noise and light sensitivity, and blurry vision), while lower in prevalence, had significantly more prognostic value with respect to the persistence of multiple symptoms over time.

Thus, further regression models were refined to include cognitive symptoms (yes/ no), emotional symptoms (yes/no), and each of the individual physical symptoms (noise, light, and vision) found to be important predictors.

In addition, the symptom of noise sensitivity was investigated further, since both hyperacusis and balance problems are indicative of vestibular damage. Although balance testing was not available for all subjects, an association was noted between those with noise sensitivity and both composite scores (from the NBM) and error scores (from the BESS). When combining balance and symptom data across all subject visits, it is apparent that those who reported sensitivity to noise at a particular visit tended to exhibit balance problems on the NBM (i.e., a lower composite score) as well as an increased number of errors on the BESS at that same visit, when compared to subjects who did not report sensitivity to noise problems (Table 17). This trend is most evident at 3 months, when error scores using the BESS were significantly higher among those reporting noise sensitivity (Table 18). Given this association and the fact that answers to questions regarding noise sensitivity were available for larger numbers of subjects, this variable (i.e., noise sensitivity) was subsequently used as an indicator of balance in the regression models.

Table 17: Association of Mean Balance Data with Symptom of Sensitivity to Noise
All Subject Visits

	Sensitive to Noise (N=29)		Not Sensitive to Noise (N=179)		
	Mean	STD	Mean	STD	p
Balance Composite	76.3	16.5	82.1	7.5	0.07
BESS Firm Errors	8.7	5.3	7.1	4.5	0.13
BESS Foam Errors	16.6	8.2	14.6	7.0	0.24
BESS Total Errors	25.3	10.7	21.7	11.0	0.17

Table 18: Association of Mean Balance Data with Symptom of Sensitivity to Noise
3 Month Data

	Sensitive to Noise (N=9)		Not Sensitive to Noise (N=38)		
	Mean	STD	Mean	STD	p
Balance Composite	70.8	27.0	82.8	5.9	0.22
BESS Firm Errors	10.0	5.6	6.7	4.3	0.15
BESS Foam Errors	20.8	7.8	13.1	6.2	0.03
BESS Total Errors	30.8	13.1	19.7	9.8	0.05

Predictors of PCS at 3 month (Table 19)s:

Significant risk factors for PCS at 3 months included the presence of emotional symptoms between 3 and 10 days post-injury (OR = 8.63) and age (OR = 7.68 for age > 40 relative to age < 26).

Table 19: Predictors of Post-Concussive Syndrome at 3 Months			
Effect	**Odds Ratio**	**Lower 95% Limit**	**Upper 95% Limit**
Vision 3-10 day	1.200	0.322	4.477
Light Sensitivity 3-10 day	2.694	0.686	11.162
Noise Sensitivity 3-10 day	2.564	0.691	9.546
Cognitive Symptoms	1.805	0.457	7.919
Emotional Symptoms	8.629	1.696	72.080
Age 26-40	3.756	0.931	16.886
Age 41+	7.677	1.769	42.007
Females	2.890	0.844	10.638
MV Mechanism	0.950	0.703	1.260
Extra-cranial injuries	1.994	0.581	7.232
Pre-injury Depression	3.130	0.737	14.982
Lifetime Alcohol Dependence	1.225	0.259	5.515
High School or less	1.805	0.587	5.693
Simple Reaction Time Thruput Mid vs. Low	1.511	0.434	5.376
Simple Reaction Time Thruput High vs. Low	1.005	0.259	3.935

Predictors of PCS at 6 months (Table 20):

For prediction of persistent symptoms at 6 months, the most significant predictor was the presence of emotional symptoms at 3-10 days (OR = 6.13). In addition, older subjects had a 7.5 times greater risk for post-concussive syndrome. Women were more than 4.5 times as likely as men to report the presence of four or more symptoms at the 6-month follow-up.

Table 20: Predictors of Post-Concussive Syndrome at 6 Months

Effect	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Vision 3-10 day	3.448	0.809	16.185
Light Sensitivity 3-10 day	0.992	0.209	4.312
Noise Sensitivity 3-10 day	2.016	0.508	8.181
Cognitive Symptoms	3.657	0.683	29.294
Emotional Symptoms	6.129	1.203	52.049
Age 26-40	1.666	0.361	8.141
Age 41+	7.511	1.635	44.459
Females	4.695	1.272	20.408
MV Mechanism	0.786	0.543	1.056
Extra-cranial injuries	1.225	0.348	4.370
Pre-injury Depression	1.010	0.237	4.004
Lifetime Alcohol Dependence	3.781	0.887	17.741
High School or less	1.150	0.330	4.036
Simple Reaction Time Thruput Mid vs. Low	1.623	0.377	7.174
Simple Reaction Time Thruput High vs. Low	3.733	0.855	18.895

Predictors of PCS at 12 months (Table 21):

The only significant predictors for those subjects still experiencing four or more symptoms at one year included the presence of emotional symptoms at 3-10 days, age greater than 26-40, and a non-motor vehicle related mechanism of injury. Because all of those with PCS at 12 months reported emotional symptoms at 3-10 days, the odds ratio could not be computed. However, the presence of emotional symptoms was deemed highly significant by conducting a likelihood ratio test.

Table 21: Predictors of Post-Concussive Syndrome at 12 months

Effect	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Vision 3-10 day	2.096	0.567	8.080
Light Sensitivity 3-10 day	1.457	0.353	6.001
Noise Sensitivity 3-10 day	2.591	0.625	11.599
Cognitive Symptoms	0.677	0.151	3.105
Age 26-40	5.871	1.288	31.263
Age 41+	2.892	0.661	14.714
Females	3.021	0.858	11.628
MV Mechanism	0.764	0.463	1.134
Extra-cranial injuries	1.391	0.400	5.050
Pre-injury Depression	1.603	0.277	8.941
Lifetime Alcohol Dependence	3.194	0.641	17.182
High School or less	0.871	0.247	2.953
Simple Reaction Time Thruput Mid vs. Low	0.950	0.201	4.392
Simple Reaction Time Thruput High vs. Low	1.105	0.222	5.709

2. To Predict Inability to Return to Work

A small percentage of individuals experience changes in occupational functioning after MTBI. Depending upon age and the nature of the person's work and their occupational environment, post concussive symptoms may greatly affect one's ability to perform work tasks. A delay in return to work or being able to stay employed but not functioning at full capacity may be noted when the work requires self initiation, complex attention, multiple sequencing, memory, concentration and mental speed processing. The diversity and unpredictability of PCS may have long term effects resulting in unemployment, in loss of advancement or the inability to fulfill all the job requirements. Severe emotional and cognitive changes may prevent one from returning to the work force. Assessing subtle changes in behavior and personality that occur following MTBI is even more challenging yet can impact everyday functioning.

Predictors of Inability to Return to Work at 3 months (Table 22):

Significant risk factors for inability to return to work at 3 months included sensitivity to noise (also indicative of balance problems, as discussed previously), (OR = 3.60), and the presence of emotional symptoms (OR = 5.87), both reported between 3 and 10 days post-injury. In addition, age was of borderline significance for age 26-40 relative to younger subjects (OR = 3.73). Interestingly, men were more likely than women (OR = 3.69) to remain away from the workplace by 3 months, although earlier models have indicated the increased likelihood of women reporting (a) more symptoms and (b) increased severity at the 3-month visit.

Table 22: Predictors of Inability to Return to Work at 3 months			
Effect	**Odds Ratio**	**Lower 95% Limit**	**Upper 95% Limit**
Vision 3-10 day	1.247	0.325	4.582
Light Sensitivity 3-10 day	0.658	0.140	2.747
Noise Sensitivity 3-10 day	3.602	1.008	13.852
Cognitive Symptoms	3.037	0.713	16.791
Emotional Symptoms	5.866	1.118	50.048
Age 26-40	3.733	0.989	15.660
Age 41+	2.187	0.556	9.338
Males	3.692	1.038	15.116
MV Mechanism	0.862	0.613	1.149
Extra-cranial injuries	1.065	0.313	3.585
Pre-injury Depression	3.788	0.923	16.696
Lifetime Alcohol Dependence	0.975	0.191	4.622
High School or less	1.310	0.421	4.018
Simple Reaction Time Thruput Mid vs. Low	1.242	0.349	4.530
Simple Reaction Time Thruput High vs. Low	1.338	0.344	5.288

Predictors of Inability to Return to Work at 6 months (Table 23):

Multivariate analysis precluded the calculation of odds ratios for emotional and cognitive symptoms due to the presence of zero cells (i.e., all subjects included in the 6-month who did not return to work reported emotional or cognitive symptoms between 3 and 10 days post injury). Hence, both variables were highly significant. In addition, subjects of age 26 to 40 had a 10.35 times greater risk for not returning to work than younger subjects.

Table 23: Predictors of Inability to Return to Work at 6 months

Effect	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Vision 3-10 day	4.646	0.726	37.419
Light Sensitivity 3-10 day	1.922	0.161	20.079
Noise Sensitivity 3-10 day	1.037	0.086	9.384
Age 26-40	10.349	1.018	268.544
Age 41+	9.235	0.836	255.900
Males	0.451	0.051	3.531
MV Mechanism	0.991	0.482	1.728
Extr-cranial injuries	1.124	0.174	8.269
Pre-injury Depression	2.487	0.244	19.685
Lifetime Alcohol Dependence	<0.001	.	2.874
High School or less	1.700	0.271	10.571
Simple Reaction Time Thruput Mid vs. Low	1.412	0.163	14.089
Simple Reaction Time Thruput High vs. Low	1.602	0.149	17.437

Predictors of Inability to Return to Work at one year:

Model results were highly unstable because the vast majority (89%) had returned to work by the 12-month follow-up visit. Therefore, a multivariate approach was not indicated.

STUDY LIMITATIONS:

- One of the limitations of the study was the relatively small number of cases for some of the statistical models. For example, it was not possible to conduct balance testing on all subjects; then, over time not all subjects returned or were interviewed at follow-up. Thus, while the total study group is 180 subjects, there are different numbers available for different subanalyses.

- Another limitation was the fact that not enough detail was obtained regarding return to work. For subjects who had a job change, whether in the same or a different company, it was not known whether this was a promotion, a chosen career path, or a change due to inability to continue in the same position as a result of the injury. If as a result of the injury, it was not known if the change was related to orthopedic restrictions or to cognitive function (i.e. mild TBI). In addition, the exact date of return to work is needed in order to further study the actual amount of time before subjects' return to work.

- There was insufficient information regarding alcohol/drug use after injury. It would be beneficial to include quantity and frequency of alcohol consumption pre-injury and at each follow-up.

- There was inadequate information on living arrangements and marital status after injury. Asking marital status and living arrangement questions 3, 6 and 12 month follow-ups would be useful for assessing social functioning overtime.

- There was a lack of speech and language pathology data after the 3 month follow-up. It would be advantageous to continue with cognitive evaluation throughout the follow-up periods to assess long term consequences of MTBI.

- No indicators of post traumatic stress disorder were measured. Since there is some overlap between the symptomatology of PTSD and mild TBI, such data might have helped to distinguish between the two.

- Also, further information regarding actual or perceived social support may have helped to determine the extent to which such support systems aided in either the ability to return to work or earlier return to work.

- It would be useful to have more detail regarding educational level, which was noted in multivariate regression models to be a significant predictor of post-concussive syndrome (those with less than high school had more symptoms). Further questions regarding whether the individual was expelled from school, had a learning disability, less social support networks, etc., might assist in understanding educational level might influence long-term symptoms following mild TBI.

- Another possible limitation is that the study was conducted in a trauma center. This may represent a bias towards the more severe end of the mild TBI spectrum; in addition, few subjects who had an isolated mild TBI. Other psychosocial factors could also be

involved, in that patients who are hospitalized may have fewer social support networks than those who may be treated and released to be cared for by family or friends.

Significance of Findings: In agreement with previous studies, women and older subjects had a higher incidence of PCS long-term. However, most studies related to long-term prognosis have focused more on physical symptoms such as headache and dizziness. From the findings reported here, those symptoms, while the most prevalent, do not have the predictive power of the cognitive and emotional symptoms. In addition, to our knowledge, no other studies of mild TBI in the literature have shown the importance of balance measures as the prediction of long-term sequelae following this injury.

These findings, if replicated, suggest the importance of screening for emotional and cognitive symptoms in the week to ten day period following the initial insult. Also, the balance tests (BESS) shown to be most predictive were the easiest to conduct, with no equipment required, only a firm surface such as a floor.

Neuropsychology testing results were not predictive in this population, at least the simple reaction time thruput, which was hypothesized to be the most useful measure. More detailed analyses of the other tests conducted may reveal additional findings, however.

The S-100β serum biomarker was not found to be predictive of PCS in this population. It was, however, associated with the presence of extracranial injuries, and the overall injury severity score**.**

Future Analyses:
The plethora of data available with this study has led to a host of other research related questions that we hope to address in the future. The topics include but are not limited to the following:

- To determine the validity of the BESS vs the Balance Master through 1 year (Correlation analysis to determine if the BESS is a low cost portable alternative to the Balance Master for detecting mild head injury)
- To determine whether some of the subscales of balance testing may be better predictors than the total error (or composite) scores
- To determine the relationship between ARES done initially and response on TBI symptom checklist at various time intervals
- To determine the relationship between ARES done at 7-10 days and TBI symptom checklist at 3, 6, and 12 months.
- To determine the change in ARES, initial to 7-10 days related to 3, 6, 12 month outcome. Can divide ARES performers into groups: those who improve v. those who stay the same or get worse.
- To determine the relationship between ARES done initially and S100β on admission
- To determine the relationship between ARES done at 3-5 and 7-10 days and S100β on admission

- To determine the relationship between ANAM at 7-10 days and adjustment measures, at 3, 6, and 12 months.
- To determine the change in ANAM over test administrations in relationship to 6 and 12 month outcome.
- To determine if ARES performance changes from initial encounter to 3-5 and 7-10 day and did improvement (or lack thereof in ARES scores) relate to persistence and severity of post concussive symptoms.
- To determine the relationship of ANAM and ARES measures given on the same day at the 7-10 day follow-up
- To determine how the mood scale from ANAM (VAS –Visual Analogue Scale) changes with time and how they relate to outcome.
- To assess the correlation of symptom clusters (cognitive, emotional and physical) with particular domains of the ANAM at different points.
- To assess the relationship between S100B and ANAM simple reaction time, procedural reaction time, and composite score (weighted thruput) over time (7-10 days through 12 months)
- To assess the relationship between S100B and effort, specifically WMT immediate recall (IR) and delayed recall (DR), over time (12 months).
- To assess differences in neuropsychological performance in TBI vs. TBI+ mood groups over time (7-10 days through 12 months)
- To assess the relationship between S100B and neuropsychological performance using hand-held PDAs (ARES).
- To determine if there is a subset of SCATBI items that could be used for a brief assessment of cognition following mild TBI
- To assess the correlation between early symptoms and admission S-100 B with cognitive outcomes as in the SCATBI
- To determine the relationship between the various depression scales used in this study
- To examine interaction terms (e.g., gender by emotional symptoms) for those regression models with sufficient numbers (e.g., PCS and return to work)
- To investigate multivariate risk factors for symptom severity using ANAM and ARES results through 7-10 days post-injury

Future Plans:

- To build on the current research findings to further refine methods to identify risk factors for PCS
- To submit grant proposals that will include Post Traumatic Stress Disorder and Neuroimaging to better understand MTBI and its sequelae

KEY RESEARCH ACCOMPLISHMENTS

- Screened 2,650 potential study participants for mild TBI
- Enrolled 180 subjects into the study
- Coordinated follow-up visits and/or telephone interviews for the following time intervals post-injury: 3-5 days, 7-10 days, 3 months, 6 months, and 12 months.
- Obtained and analyzed blood samples for 168 of the 180 subjects
- Conducted neuropsychology and speech testing on subjects.
- Conducted balance testing on all patients medically able to complete the tests.
- Obtained follow-up evaluations for 61%, 59% and 57% of subjects at 3-, 6- and 12-months post-injury, respectively.
- Completed a descriptive analysis of symptoms at each of the follow-up visits.
- Completed an analysis of baseline predictors of persistent post-concussive symptoms, lack of general well being and inability to return to work.
- Presented eight posters at professional meetings
- Submitted two grant applications to USAMRMC in May 2006
- Submitted one manuscript on preliminary three month findings.

REPORTABLE OUTCOMES

Abstracts Presented (Appendix A):

Dischinger PC, Cooper C, Mackenzie, Romani W, Spector J: Serial Assessment of Mild Head Injury: Early Predictors of Outcome, Department of Defense Military Health Research Forum, San Juan Puerto Rico, April 25-28, 2004

Lee-Wilk, Terry, Dischinger, P.C., Mackenzie, C.F., Murdock, K.R., Imle, P.I., Spector, J., Kufera, J.A., Auman, K.M., Thysen, J., and Kane, R.L. The Relationship Between S100B Protein and Neuropsychological Performance in Mild Traumatic Brain Injury. Poster presentation at the annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

Thysen, J., Lee-Wilk, T., Mackenzie, C., Kane, R.L., Spector, J., Auman, K.M., Kufera, J.A., Murdock, K.R., Imle, P.I., and Dischinger, P.C. The Relationship Between S100B Protein Levels and Effort in Mild Traumatic Brain Injury. Poster presentation at the annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

Dischinger PC, Cooper CC, Kane RL, Mackenzie C, Romani W, Ryb GE and SAMHI Research Team: Mile Traumatic Brain Injury: Predictors of Long-term Outcomes, Department of Defense Military Health Research Forum, San Juan Puerto Rico, May 2006

Lee-Wilk, T; Kane, RL.; Mackenzie, C; Spector, J; Murdock, KR; Kufera, JA; Auman, KM; Imle, PC; Thysen, J; Lonser, K; Dischinger, PC: The Effects of Depression and Anxiety on Neuropsychological Performance in Mild Traumatic Brain Injury, American Psychiatric Association Annual Meeting, Toronto Canada, May 2006

Ryb GE, Cooper, C, Dischinger PC, Auman KM, Kane RL, Lee-Wilk T, Murdock, KR, Imle C: Predictors of Post-Concussive Symptoms at Three Months, Poster presentation at the American Association for the Surgery of Trauma (AAST)65th Annual Meeting New Orleans, LA, September 2006.

Gabriel E. Ryb, MD, MPH *; Carnell Cooper, MD *, Patricia C. Dischinger, PhD; Kimberly M. Auman, MS; Robert L. Kane, PhD; Terry Lee-Wilk, PhD; Karen Murdock, BSPT; Cris Imle, BSPT

Bercaw, E. L., Lee-Wilk, T., Kufera, J., Auman, K., Murdock, K., Imle, P., Dischinger, P., Mackenzie, C., Cernich, A., Stern, S., Wulff, L., Spector, J., Kane, R. Effects of Overall Injury Severity on ANAM Performance in Mild Traumatic Brain Injury. Poster presented at the annual meeting of the International Neuropsychological Society, Portland, OR, February 2007.

Manuscripts Submitted:

Ryb GE, Cooper C, Dischinger PC, Auman KM, Kane RL, Lee-Wilk T, Murdock, KR, Imle C: Predictors of Post-Concussive Symptoms at Three Months, Submitted to the Journal of Trauma, Fall 2006. Not Accepted

Grant Proposals Submitted:

A Multidisciplinary Evaluation of Mild Traumatic Brain Injury: Biological, Cognitive and Clinical Predictors of Outcome. Submitted to USAMRMC, 2006. Not Funded

Predictors of Post Traumatic Stress Disorder (PTSD) in a Population of Motor Vehicle Trauma Patients. Submitted to USAMRMC, 2006. Not Funded

CONCLUSIONS

Although the literature is replete with studies of mild TBI, most are descriptive in nature, documenting symptoms over time, either for one week, one month, or up to two years following the injury. Few studies have addressed which factors, including symptoms, are prognostic of long-term sequelae of mild TBI; those that have usually focused on the more prevalent symptoms such as headache.

Findings from this research reveal that these more prevalent physical symptoms peak in the week or so following the injury, then decline, returning to baseline levels by 3 months post-injury. In addition, these physical symptoms, with the exception of noise sensitivity, are not significant risk factors for post-concussive syndrome. Cognitive and emotional symptoms, however, were found to be much more prognostic of long-term sequelae (PCS); this is especially true for the post-injury emotional symptoms of anxiety, depression, and irritability.

Despite the relatively small number of subjects with balance testing (due to associated injuries precluding testing), findings from the BESS were noted to be significantly associated with emotional symptoms at 3 months and physical symptoms at 6 months post-injury. In addition, the BESS was significantly associated with PCS at the 3 month follow-up. That is, subjects who had more errors on the BESS test, especially the "firm" component (standing on the floor), were significantly more likely to report having four or more symptoms at 3 months. Further analyses also revealed an association between the balance test results and the physical symptom of noise sensitivity, perhaps suggesting vestibular injury.

As shown in previous studies, women and older patients were also at increased risk of PCS at subsequent follow-up intervals.

The S-100β test was not found to be a useful predictor of PCS in this trauma patient population, perhaps because of its high association with other extracranial injuries, especially fractures. In addition, the simple reaction time from the ANAM was not found to be a significant predictor of persistent symptomatology. Data from the other ANAM test, such as the Mood Scale, may prove to be more useful in predicting those with long-term symptoms.

Overall, 89.3% of subjects who were employed or in school before their injury had returned to work by 1 year. While only 13.7% had returned by 7-10 days, by three months approximately two thirds had returned. By six months most of those who would eventually return to pre-injury functioning had already done so(88.2%).

At three months, those unable to return to work included those with noise sensitivity and/ or emotional symptoms at 3-10 days post-injury. In addition, older subjects and men were less likely to return to employment/ work. By six months, both emotional and cognitive symptoms reported post-injury were significant predictors as was increasing age.

REFERENCES

Adamowich B, Henderson J. SCATBI (*Scales of Cognitive Ability for Traumatic Brain Injury).* Normed ed. New York: Riverside Publishing Co; 1992.

Alexander MP. Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. *Neurology.* 1995;45:1253-1260.

Alfano MS, & Satz P. Commentary and perspectives on R. M. Allen's "The test performance of the brain injured". *Journal of Clinical Psychology.* 2000;56:975-997.

Alves W, Colohan A, O'Leary T, Rimel R, Jane J: Understanding posttraumatic symptoms after minor head injury. *J Head Trauma Rehabil.* 1986;1(2):1-12.

Alves W, Macciocchi SN, Barth, JT. Postconcussive symptoms after uncomplicated mild head injury. *J Head Trauma Rehabil.* 1993;8:48-59.

Anderson RE, Hansson LO, Nilsson O, Dijlai-Merzoug R, Settergren G. High serum S100B levels for trauma patients without head injuries. *Neurosurgery.* 2001;48:1255-8 discussion.

Asikainen I, Kaste M, Sarna S. Patients with traumatic brain injury referred to a rehabilitation and re-empoyment programme: social and professional outcome for 508 Finnish patients 5 or more years after injury. *Brain Injury.* 1996 Dec;10(12):883-99.

Assaf Y, Beit-Yannai E, Shohami E, Berman E, Cohen Y. Diffusion- and T2-wieghted MRI of close-head injury in rats: a time course study and correlation with histology. *Magn Reson Imaging.* 1997;15:77-85.

Bailes JE, Hudson V. Classification of sport-related head trauma: a spectrum of mild to severe injury. *Journal of Athletic Training.* 2001;36(3):236-243.

Barth JT, Macciocchi SN, Giordani B, Rimel R, Jane JA, Boll TJ. Neuropsychological sequelae of minor head injury. *Neurosurgery.* 1983;13(5):529-532.

Bartnik BL, Kendall EJ, Obenaus A. Cortical devascularization: quantitative diffusion weighted magnetic resonance imaging and histological findings. *Brain Res.* 2001;915:133-142.

Basford JR, Chou L-S, Kaufman KR, Brey RH, Walker A, Malec JF, et al. An assessment of gait and balance deficits after traumatic brain injury. *Arch Phys Med Rehabil.* 2003;84:343-349.

Bazarian JJ, Atabaki S. Predicting postconcussion syndrome after minor traumatic brain injury. *Academic Emergency Medicine.* 2001;8(8):788-795. *

Bazarian J, Hartman M, Delahunta E. Minor head injury: predicting follow-up after discharge from the emergency department. *Brain Inj.* 2000;14:285-294.*

Bazarian J, McClung J, Shah M, Cheng Y, Flesher W, Kraus J. Mild traumatic brain injury in the United States, 1998-2000. *Brain Inj.* 2005;19(2):85-91.*

Bazarian JJ, Zemlan FP, Mookerjee S, and Stigbrand T. Serum S-100B and cleaved-tau are poor predictors of long-term outcome after mild traumatic brain injury. *Brain Inj.* 2006;20(7):759-765.

Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *JINS.* 2005;11:215-227.

Bernstein DM. Information processing difficulty long after self-reported concussion. *JINS.* 2002;8:673-682.

Binder LM, Rohling ML, Larrabee J. A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *J Clin Exp Neuropsychol.* 1997;19:421-431.

Black K, Safonte R, Millis S, Desantis N, Harrison-Felix C, Wood D et al. Sitting balance following brain injury: Does it predict outcome? *Brain Inj.* 2000;24:141-152.

Bleiberg J, Garmoe WS, Halpern EL, Reeves DL, Nadler JD. Consistency of within-day and across-day performance after mild brain injury. *Neuropsychiatry Neuropsychol Behav Neurol.* 1997;10(4):247-253.

Bleiberg J, Halpern EL, Reeves D, Daniel JC. Future directions for the neuropsychological assessment of sports concussion. *J Head Trauma Rehabil.* 1998;13(2):36-44.

Bleiberg J, Kane RL, Reeves DL, Garmoe WS, Halpern E. Factor analysis of computerized and traditional tests used in mild brain injury research. *The Clinical Neuropsychologist.* 2000;14:287-294.

Blostein P and Jones SJ. Identification and evaluation of patients with mild traumatic brain injury: results of a national survey of Level I trauma centers. *J Trauma.* 2003;55(3):450-453.

Boake C, High WM. Functional outcome from traumatic brain injury: Unidimensional or multidimensional? *Am J Phys Med Rehabil*. 1996;75:105-113.

Boake C, McCauley SR, Pedroza C, Levin HS, Brown SA, Brundage SI. Lost productive work time after mild to moderate traumatic brain injury with and without hospitalization. *Neurosurgery*. 2005;56:994-1003discussion.

Boake C, Mills SR, High WM, Delmonico RL, Kreutzer JS, Rosenthal M, Sherer M, Ivanhoe CB. Using early neuropsychological testing to predict long-term productivity outcome from traumatic brain injury. *Arch Phys Med Rehabil*. 2001;82:761-768.*

Bohnen N, Jolles J, Twijnstra A. Neuropsychological deficits in patients with persistent symptoms six months after mild head injury. *Neurosurgery*. 1992;30:692-695.

Bohnen NI, Jolles J, Twijnstra A, Mellink R, Wijnen G. Late neurobehavioural symptoms after mild head injury. *Brain Inj*. 1995;9:27-33.

Bohnen N, Van Zutphen W, Twijnstra A, Wijnen G, Bongers J, Jolles J. Late outcome of mild head injury" results from a controlled postal survey. *Brain Inj.* 1994;8:701-708.*

Borczuk P. Predictors of intracranial injury in patients with mild head trauma. *Ann Emerg Med*. 1995;25:731-736.*

Borg J, Holm L, Cassidy D, Peloso P, Carroll L, Holst H, et al. Diagnostic procedures in mild traumatic brain injury. *J Rehabi Med.* 2004;43:61-75.

Borgaro SR, Prigatano GP, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. *Brain Inj.* 2003;17:189-198.*

Bowden SC, Shores EA, Mathias JL. Does effort suppress cognition after traumatic brain injury? A re-examination of the evidence for the Word Memory Test. *Clinical Neuropsychologist*. 2006;20(4):858-872.

Bowman ML. Ecological validity of neuropsychological and other predictors following head injury. *The Clinical Neuropsychologist*. 1996;10:382-396.

Brooks J, Fos LA, Greve KW, Hammond JS. Assessment of executive function in patients with mild traumatic brain injury. *J Trauma*. 1999;46:159-163.

Brenneman, FD, Boulanger, BR, McLellan, BA, Redelmeier DA. Measuring injury severity: time for a change? *J Trauma*. 1998;44:580-582.

Brewer TL, Metzger BL, Therrien B. Trajectories of cognitive recovery following a minor brain injury. *Research in Nursing & Health*. 2002;25:269-281.

Bryant R, Harvey A, Guthrie R, Moulds M. A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *J Abnorm Psychol.* 2000;109(2):341-344.*

Bryant RA, Harvey AG. Postconcussive symptoms and posttraumatic stress disorder after mild traumatic brain injury. *J Nerv Ment Dis*. 1999;187:302-305.

Burgess P, Alderman N, Evans J, Emslie H, Wilson B. The ecological validity of tests of executive function. *J Int Neuropsychol Soc*. 1998;4:457-558.

Campbell M, Parry A. Balance disorder and traumatic brain injury: Preliminary findings of a multi-factorial observational study. *Brain Inj.* 2005;19:1095-1104.*

Cantu R. Posttraumatic retrograde and anterograde amnesia: pathophysicology and implications in grading and safe return to play. *Journal of Athletic Training.* 2001;36(3):2440248.

Cavanaugh JT, Guskiewicz KM, Giuliani C, Marshall S, Mercer VS, Stergiou N. Recovery of postural control after cerebral concussion: new insights using approximate entropy. *J Athl Train.* 2006;41:305-313.*

Centers for Disease Control (CDC) and Prevention. Report to Congress on mild traumatic brain injury in the Unites States: Steps to prevent a serious public health problem. Atlanta, GA: U.S. Department of Health and Human Services, 2003.

Chambers J, Cohen SS, Hemminger L, Prall JA, Nichols JS. Mild traumatic brain injuries in low-risk trauma patients. *Journal of Trauma.* 1996;41(6):976-980.

Chamelian L, Feinstein A. Outcome after mild to moderate traumatic brain injury: The role of dizziness. *Arch Phys Med Rehabil.* 2004;85(10):1662-1666.

Chan RC. Sustained attention in patients with mild traumatic brain injury. *Clin Rehabil*. 2005a;19:188-193.*

Chan RC. How severe should symptoms be before someone is said to be suffering from post-concussion syndrome? An exploratory study with self-reported checklist using Rasch analysis. *Brain Inj*. 2005b;19:1117-1124.

Collins MW, Field M, Lovell MR, Iverson G, Johnston KM, Maroon J, Fu, F. Relationship between postconcussion headache and neuropsychological test performance in high school athletes. *Am J Sports Med*. 2003;31(2):168-173.

Collins MW, Lovell MR, Mckeag DB. Current issues in managing sport-related concussion. *JAMA.* 1999;282(24):2283-2285.

Crepeau F, Scherzer P. Predictors and indicators of work status after traumatic brain injury: A meta-analysis. *Neuropsychol Rehabil*. 1993;3:5-35.

Cushman JG, Agarwal N, Fabian TC, Garcia V, Nagy KK, Pasquale MD, Salotto AG. *Practice management guidelines for the management of mild traumatic brain injury: the EAST practice management guidelines work group*. Eastern Association for the Surgery of Trauma, 2001.

Daniel JC, Olesniewicz MH, Reeves DL, Tam D, Bleiberg J, Thatcher R, et al. Repeated measures of cognitive processing efficiency in adolescent athletes: implications for monitoring recovery from concussion. *Neuropsychiatry Neuropsychol Behav Neurol.* 1999; 12(3):167-169.

Davidoff G, Roth E, Thomas P, Doljanac R, Dijkers M, Berent S, et al. Depression and neuropsychological test performance in acute spinal cord injury patients: lack of correlation. *Arch Clin Neuropsychol*. 1990;5:77-88.

de Krujik J, Leffers P, Menheere P, Meerhoff S, Rutten J, Twijnstra A. Prediction of post-traumatic complaints after mild traumatic brain injury: early symptoms and biochemical markers. *J Neurol Neurosurg Psychiatry.* 2002;73:727-732.

de Kruijk JR, Twijnstra A, Leffers P. Diagnostic criteria and differential diagnosis of mild traumatic brain injury. *Brain Inj.* 2001;15:99-106.

Deb S, Lyons I, Koutzoukis C. Neurobehavioral symptoms one year after a head injury. *Br J Psychiatry.* 1999;174:360-365.*

Deb S, Lyons I, Koutzoukis C. Neuropsychiatric sequelae one year after a minor head injury. *J Neurol Neurosurg Psychiatry*. 1998;65:899-902.

deBoussard C, Fredman P, Lundin A, Andersson K, Edman G, Borg J. S100 in mild traumatic brain injury. *Brain Inj*. 2004;18:671-683.

DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. *N Engl J Med.* 2005;352:1335-42.

Dikmen S, Machamer J, Temkin N. Mild head injury: Facts and artifacts. *J Clin Exp Neuropsychol*. 2001;23:729-738.

Dikmen S, McLean A, Temkin N. Neuropsychological and psychosocial consequences of minor head injury. *J Neurol Neurosurg Psychiatry.* 1986;49:1227-1232.

Dikmen SS, Temkin NR, Machamer JE, Holubkov AL, Fraser RT, Winn R. Employment following traumatic brain injuries. *Arch Neurol*. 1994;51:177-186.*

Duff MC, Proctor A, Haley K. Mild traumatic brain injury (MTBI): assessment and treatment procedures used by speech-language pathologists (SLPs). *Brain Inj*. 2002;16(9):773-787.

Dupuy HJ. The Psychological General Well-Being (PGWB) Index. In : Wenger nk, Mattson ME, Furberg CD, Elinson J, eds. Assessment of quality of life in clinical trials of cardiovascular therapist. New York: LeJacq. 1984:170-183.

Edna TH. Disability 3-5 years after minor head injury. *J Oslo City Hosp.* 1987;37(5):41-48.

Elsmore T, Reeves D. ANAM readiness evaluation system (ARES): User's guide. *Activity Research Services.* 2002, 2004

Elsmore TF, Reeves DL, Reeves AN. The ARES test system for palm OS handheld computers. *Archives of Clinical Neuropsychology.* 2007 Feb;22S1: S135-144.

Ernst A, Basta D, Seidl RO, Todt I, Scherer H, Clarke A. Management of posttraumatic vertigo. *Otolaryngol Head Neck Surg.* 2005;132:554-558.*

Evans RW. The postconcussion syndrome and the sequelae of mild head injury. *Neurologic Clinics.* 1992;10:815-847. *

Ewing JA. Detecting alcoholism: the CAGE questionnaire. *JAMA.* 1984;252:1905-1907.

Feinstein A, Rapoport M. Mild traumatic brain injury: The silent epidemic. *Can J Public Health*. 2000;91:325-326.*

Ferguson RJ, Mittenberg W, Barone DF, Schneider B. Postconcussion syndrome following sports-related head injury: Expectation as etiology. *Neuropsychology*. 1999;13:582-589.

Frencham KAR, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *J Clin Exp Neuropsychol*. 2005;27:334-351.

Gennarelli TA, Spielman GM, Langfitt TW, Gildenberg PL, Harrington T, Jane JA. Influence of the type of intracranial lesion on outcome from severe head injury. *J Neurosurg*. 1982;56(1):26-32.

Gentilini M, Nichelli P, Schoenhuber R, Bortolotti P, Tonelli L, Falasca A, et al. Neuropsychological evaluation of mild head injury. *J Neurol Neurosurg Psychiatry.* 1985;48:137-140.

Geurts ACH, Ribbers GM, Knoop JA, van Limbeek J. Identification of static and dynamic postural instability following traumatic brain injury. *Archives of Physical Medicine and Rehabilitation.* 1996;77:639-644.

Green P. The pervasive influence of effort on neuropsychological tests. *Physical Medicine and Rehabilitation Clinics of North America*. 2007;18(1):43-68.

Green P, Allen LM, and Astner, K: The Word Memory Test: A User's Guide to the Oral and Computer-Administered Forms, US Version 1.1. Durham, NC: CogniSyst, Inc. 1996.

Green P, Iverson GL, Grant L, Allen L. Detecting malingering in head injury litigation with the Word Memory Test. *Brain Inj*. 1999;13(10):813-819.

Green P, Rohling ML, Lees-Haley PR, Allen LM. Effort has a greater effect on test scores than severe brain injury in compensation claimants. *Brain Inj*. 2001;15:1045-1060.

Greenspan, L., McLellan, B. A., Greig, H. Abbreviated injury scale and injury severity score: a scoring chart. *J Trauma*. 1985;25:60-64.

Greenspan AI, Wrigley JM, Kresnow M, Branche-Dorsey C, Fine P. Factors influencing failure to return to work due to traumatic brain injury. *Brain Inj*. 1996;10:207-218.

Gronwall D, Wrightson P. Delayed recovery of intellectual function after minor head injury. *Lancet.* 1974;2(7881):605-609.

Gronwall D. Cumulative and persisting effects of concussion on attention and cognition. *Mild Head Injury*. Levin HS, Eisenberg HM, Benton AL (eds). New York: Oxford University Press; 1989.

Groswasser Z, Reider-Groswasser I, Schwab K, Ommaya A, Pridgen A, Brown H, et al. Quantitative imaging in late TBI. Part II: Cognition and work after closed and penetrating head injury: A report of the Vietnam head injury study. *Brain Inj*. 2002;16:681-690.

Grote CL, Kooker EK, Garron DC., Nyenhuis DL, Smith CA, and Mattingly ML. Performance of compensation seeking and non-compensation seeking samples on the Victoria Symptom Validity Test: Cross-validation and extension of a standardization study. *Journal of Clinical and Experimental Neuropsychology*, 2000;22(6):709-719.

Gurka JA, Felmingham KL, Baguley IJ, Schotte DE, Crooks J, Marosszeky JE. Utility of the Functional Assessment Measure after discharge from inpatient rehabilitation. *J Head Trauma Rehabil*. 1999;14:247-256.

Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery.* 2005;57:719-726;discussion 719-726.*

Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: The NCAA Concussion Study. *JAMA* 2003;290:2549-2555.*

Guskiewicz KM, Perrin DH, Gansneder BM. Effect of mild head injury on postural stability in athletes. *J Athl Train*. 1996;31:300-306.*

Guskiewicz K, Perrin D. Research and Clinical Applications of Assessing Balance. *J Sport Rehabil.* 1996;5:45-63.*

Guskiewicz KM, Riemann BL, Perrin DH, Nashner LM. Alternative approaches to the assessment of mild head injury in athletes. *Med Sci Sports Exerc*. 1997;29:S213-221.

Guskiewicz KM, Ross SE, Marshall, SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. *J Athl Train.* 2001;36(3):263-73.

Guskiewicz KM, Weaver NL, Padua DA, Garrett WI. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med.* 2000;28:643-650.

Hanlon RE, Demery JA, Martinovich Z, Kelly JP. Effects of acute injury characteristics on neurophysical status: Vocational outcome following mild traumatic brain injury. *Brain Inj*. 1999;13(11):873-887.

Harris WC, Hancock PA. Field assessment of cognitive performance under stress. *Proceedings of the Human Factors and Ergonomics Society* 47th annual meeting, Denver, CO, October, 2003.

Hartlage, LC, Durant-Wilson D, Patch PC. Persistent neurobehavioral problems following mild traumatic brain injury. *Arch Clin Neuropsychol*. 2001;16:561-570.

Husum H, Strada G. Injury severity score versus new injury severity score for penetrating injuries. *Prehospital and Disaster Medicine*. 2002;17:27-32.

Huynh T, Jacobs DG, Dix S, Sing RF, Miles WS, Thomason MH. Utility of neurosurgical consultation for mild traumatic brain injury. *The American Surgeon.* 2006;72:1162-1167.

Ingebrigtsen T, Romner B. Biochemical markers of traumatic brain injury. *J Trauma.* 2002;52(4):799-808.*

Ingebrigtsen T, Romner B. Serial S-100 protein serum measurements related to early magnetic resonance imaging after minor head injury. *J Neurosurg*. 1996;85:945-948.*

Ingebrigsten T, Romner B, Kongstad P, Langbakk B. Increased serum concentrations of protein S-100 after minor head injury: A biochemical serum marker with prognostic value? *J Neurol Neurosurg Psychiatry*. 1995;59:103.*

Ingebrigtsen T, Romner B, Marup-Jensen S, et al. The clinical value of serum S-100 protein measurements in minor head injury: A Scandinavian multicenter study. *Brain Inj.* 2000;14:1047-1055.*

Ingebrigtsen T, Romner B, Trumpy JH. Management of minor head injury: the value of early computed tomography and serum protein S-100 measurements. *J Clin Neurosci*. 1997;45:29-33.*

Ingebrigtsen T, Waterloo K, Jacobsen EA, LKangbakk B, Romner B. Traumatic brain damage in minor head injury" relation of serums-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. *Neurosurgery.* 1999;45:468-476.

Ingebrigtsen T, Waterloo K, Marup-Jensen S, Attner E, Romner B. Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. *J Neurology.* 1998;245:609-612.

Ingersoll CD, Armstrong CW. The effects of closed-head injury on postural sway. *Med Sci Sports Exerc.* 1992;24(7):739-743.

International Classification of Diseases, 10th Revision (ICD-10). Geneva (Switzerland): World Health Organization. 2001.

Iverson GL, Lovell MR, Smith SS. Does brief loss of consciousness affect cognitive functioning after mild head injury? *Arch Clin Neuropsychol.* 2000;15:643-648.

Iverson GL. Outcome from mild traumatic brain injury. *Current Opinion in Psychiatry*. 2005;18:301-317.

Ivins BJ, Schwab KA, Warden D, Harvey S, Moilien M, Powell J, et al. Traumatic brain injury in U. S. Army paratroopers: Prevalence and character.
J Trauma. 2003;55:617-621.

Jansen EC, Larsen RE, Olesen MB. Quantitative Romberg's test. Measurement and computer calculation of postural stability. *Acta Neurol Scand.* 1982;66:93-99.*

Jeret JS, Mandell M, Anziska B, Lipitz M, Vilceus AP, Ware JA, Zesiewicz TA. Clinical predictors of abnormality disclosed by computed tomography after mild head trauma. *Neurosurgery*. 1993;32:9-15.

Joseph S, Masterson J. Posttraumatic stress disorder and traumatic brain injury: Are they mutually exclusive? *Journal of Traumatic Stress*. 1999;12: 437-453.

Kabat MH, Kane RL, Jefferson AL, DiPino RK. Construct validity of selected Automated Neuropsychological Assessment Metrics (ANAM) battery measures. *Clin Neuropsychol.* 2001;15(4):498-507.*

Kane RL, Kay GG. Computerized assessment in neuropsychology: A review of tests and test batteries. *Neuropsychol Rev.* 1992;3(1):1-117.*

Kane RL, & Reeves DL. (1997). Computerized test batteries. In A. Horton (Ed.) *The neuropsycholgical handbook: New edition (Vol. 2).* New York: Springer*

Kane RL, Roebuck-Spender T, Short P, Kabata M, Wilken J. Identifying and monitoring cognitive deficits in clinical populations using automated neuropsychological assessment metrics (ANAM) tests. *Arch Clin Neuropsychol*. 2007;22S1:S115-S126.

Keyser MA, Bricout JC, Wehman P, Campbell LR, Cifu DX, Englander J, et al. Acute predictors of return to employment after traumatic brain injury: A longitudinal follow-up. *Arch Phys Med Rehabil*. 2002;83:635-640.

Klonoff PS, Watt LM, Dawson LK, Henderson SW, Gehrels J, Wethe JV. Psychosocial outcomes 1-7 years after comprehensive milieu-oriented neurorehabilitation: The role of pre-injury status. *Brain Inj*. 2006;20(6):601-612.

Korfias S, Stranjalis G, Psachoulia C, Vasiliadis C, Pitardis M, Boviatsis E, et al. Slight and short-lasting increase of serum S-100B protein in extra-cranial trauma. *Brain Inj*. 2006;20(8):867-872.

Kraus J, Schaffer K, Ayers K, Stenehjem J, Shen H, Afifi AA. Physical complaints, medical service use, and social employment changes following mild traumatic brain injury. *J Head Trauma Rehabil.* 2005;20(3):239-256.

Kreutzer JS, Marwitz J, Walker W, Sander AM, Sherer M, Bogner J,et al. Bushnik T. Moderating factors in return to work and job stability after traumatic brain injury. *J Head Trauma Rehabil*. 2003;18:128-138.

Kumar S, Rao SL, Nair RG, Pillai S, Chandramouli BA, Subbakrishna DK. Sensory gating impairment in development of post-concussive symptoms in mild head injury. *Psychiatry and Clinical Neurosciences*. 2005;59:466-472.

Kurtzke JF, Jurland LT: The epidemiology of neurologic disease. In: Joynt RJ, editor. *Clin NeurolRev*. Philadelphia: JB Lippincott; 1993.

Langlois JA, Rutland-Brown W, Thomas KE. *Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths.* Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

Langlois JA, Sattin RW: Traumatic brain injury in the United States: research and programs of the Centers for Disease Control and Prevention (CDC). *J Head Trauma Rehabil*. 2005; 20:187-188.

Landre N, Poppe CJ, Davis N, Schmaus B, Hobbs SE. Cognitive functioning and post-concussive symptoms in trauma patients with and without mild TBI. *Arch Clin Neuropsychol*. 2006;21:255-273.

Larrabee GJ. Neuropsychology in personal injury litigation. *Journal of Clinical and Experimental Neuropsychology*. 2000;22:702-707.

Lavoie A, Moore L, LeSage N, Liberman M, Sampalis JS. The injury severity score or the new injury severity score for predicting intensive care unit admission and hospital length of stay? *Injury.* 2005;36:477-483.

Lavoie A, Moore L, LeSage N, Liberman M, Sampalis JS. The new injury severity score: a more accurate predictor of in-hospital mortality than the injury severity score. *J Trauma.* 2004;56:1312-1320.

Leininger BE, Gramling SE, Farrell AD, Kreutzer JS, Peck EA. III Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. *J Neurol Neurosurg Psychiatry.* 1990;53:293-296.

Lepers R, Bifard AX, Diard JP, Gouteyron JF, Guezenned CY. Fatigue effects on body balance. *Eur J Appl Phusiol Occup Physiol.* 1997;76:55-61.

Levin H, O'Donnell V, Grossman RG. The Galveston orientation and amnesia test: A practical scale to assess cognition after head injury. *J Nerv Ment Dis.* 1979;167:675-684.

Levin HS. *Mild Head Injury.* Levin HS, Eisenberg HM, Benton AL, eds. New York: Oxford University Press; 1989

Levinson DM, Reeves DL. Monitoring recovery from traumatic brain injury using Automated Neuropsychological Assessment Metrices (ANAM V1.0). *Arch Clin Neuropsychol.* 1997;12:155-166.*

MacFlynn G, Montgomery EA, Fenton GW, Rutherford W. Measurement of reaction time following minor head injury. *J Neurol Neurosurg Psychiatry.* 1984;47:1326-1331.

Mahon D, Elger C. Analysis of posttraumatic syndrome following mild head injury. *J Neurosci Nurs.* 1989;21(6):382-384.

Malec J. Impact of comprehensive day treatment on societal participation for persons with acquired brain injury. *Arch Phys Med Rehabil.* 2001;82:885-895.

Mancuso JJ, Guskiewicz KM, Onate JA, Ross SE. An investigation of the learning effect of the balance error scoring system and its clinical implications [abstract]. *J Athl Train.* 2002; 37:S-10.

Martelli MF, Grayson RL, Zasler ND. Posttraumatic headache: neuropsychological and psychological effects and treatment implications. *J Head Trauma Rehabil.* 1999;14(1):49-69.

Marwitz J. (2000) The Neurobehavioral Functioning Inventory. *The Center for Outcome Measurement in Brain Injury*. http://www.tbims.org/combi/nfi (accessed April 25, 2006).

Mathias JL, Beall JA, Bigler ED. Neuropsychological and information processing deficits following traumatic brain injury. *J Int Neuropsychol Soc*. 2004;10:286-297.

Matser EJ, Kessels AG, Lezak MD, Jordan BD, Troost J. Neuropsychological impairment in amateur soccer players. *JAMA.* 1999;282(10):971-973.

Max W, MacKenzie EJ, Rice DP. Head injuries: costs and consequences. *J Head Trauma Rehabil.* 1991;6:76-91.

McAllister TW, Sparling MB, Flashman LA, Guerin SJ, Mamourian AC, Saykin AJ. Differential working memory load effects after mild traumatic brain injury. *Neuroimage*. 2001;14:1004-1012.

McCauley SR, Boake C, Levin HS, Contant CF, Song JX. Postconcussional disorder following mild to moderate traumatic brain injury: Anxiety, depression, and social support as risk factors and comorbidities. *J Clin Exp Neuropsychol.* 2001;23(6):792-808.

McCrea M, Guskiewicz KM, Barr W, Marshall SW, Randolph C Cantu R, et al. Acute effects and recovery time following concussion in collegiate football players: The NCAA concussion study. *JAMA.* 2003;290(19):2556-2563.*

McCullagh S, Oucherlony D, Protzner A, Blair N, Feinstein A. Prediction of neuropsychiatric outcome following mild traumatic brain injury: An examination of the Glasgow Coma Scale. *Brain Inj.* 2001;15(6):489-497.

McDowell I, Newell C. Psychological Well Being. Measuring Health A Guide to Rating Scales and Questionnaires. New York: Oxford University Press, 1996:177-237.

McFadyen BJ, Swaine B, Sumas D, Durand A. Residual effects of traumatic brain injury on locomotor capacity. *J Head Trauma Rehabil.* 2003;18:512-525.*

Meares S, Shores EA, Batchelor J, Baguley IJ, Chapman J, Gurka J, et al. The relationship of psychological and cognitive factors and opioids in the developments of the postconcussion syndrome in general trauma patients with mild traumatic brain injury. *J Int Neuropsychol Soc*. 2006;12:792-801.

Middleboe T, Anderson HS, Birket-Smith M, Friis ML. Minor head injury: Impact on general health after one year. A prospective follow-up study. *Acta Neurol Scand*. 1992;85: 5-9.*

Miller LJ, Mittenberg W. Brief cognitive behavioral interventions in mild traumatic brain injury. *Applied Neuropsychology.* 1998;5(4):172-183.

Mittenberg W, Canyock EM, Condit D, Patton D. Treatment of post-concussion syndrome following mild head injury. *J Clin Exp Neuropsychol.* 2001;23:829-836.*

Mittenberg W, Strauman S. Diagnosis of mild head injury and the postconcussion syndrome. *J Head Trauma Rehabil.* 2000;15:783-791.*

Mittl RL, Grossman RI, Hiehle JF, Kauder DR, Gennarelli TA, Alberger GW. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol.* 1994;15:1583-1589.

Mooney G, Speed J, Sheppard S. Factors related to recovery after mild traumatic brain injury. *Brain Inj.* 2005;19:975-987.

Moore BW, McGregor D. Chromatographic and electrophoretic fractionation of soluble proteins of brain and liver. *J Biol Chem*. 1965;240:1647-1653.

Moore EL, Terryberry-Spohr L, Hope DA. Mild traumatic brain injury and anxiety sequelae: a review of the literature. *Brain Injury.* 2006 Feb;20(2):117-32.

Mullin J, Ripley D, Vargas J, Godshall R, Korrick S. Relationship between balance and cognition following traumatic brain injury. *Premier Outlook.* 2002;3:30-35.

Naemi ZS, Weinhofer A, Sarahrudi K, Heinz T, Vecsei V. Predictive value of S-100B protein and neuron specific enolase as markers of traumatic brain damage in clinical use. *Brain Inj*. 2006;20(5):463-468.

Nygren de Boussard C, Lundin A, Karlstadt D, Edman G, Bartfai A, and Borg J. S100 and cognitive impairment after mild traumatic brain injury. *J Rehabil Medicine*. 2005;37:53-57.*

Nylen K, Ost M, Csajbok LZ et al. Increased serum-GFAP in patients with severe traumatic brain injury is related to outcome. *J Neurol Sci*. 2005;240:85-91.

O'Shaughnessy EJ, Fowler RS, Reid V. Sequelae of mild closed head injuries. *J Fam Pract.* 1984;18(3):391-394.

Ommaya AK, Ommaya AK, DannenbergAL, Salazar AM. Causation, incidence, and costs of traumatic brain injury in the U.S. military medical system. *J Trauma.* 1996;40(2):211-217.

Ommaya AK, Salazar AM, Dannenberg AL, Ommaya AK, Chervinsky AB, Schwab K. Outcome after traumatic brain injury in the U.S. military medical system. *J Trauma.* 1996;41(6):972-975.

Onate JA, Guskiewicz KM, Riemann BL, Prentice WE. A comparison of sideline versus clinical cognitive test performance in collegiate athletes. *J Athl Train.* 2000;35:155-160.*

Osler T, Baker SP, Long W. A modification of the injury severity score that both improves accuracy and simplifies scoring. *J Trauma*. 1997;43:922-926.

Ownsworth T, McKenna K. Investigation of factors related to employment outcome following traumatic brain injury: A critical review and conceptual model. *Disability and Rehabilitation*. 2004;26(13):765-784.

Ownsworth T, Desbois J, Fleming J, Strong J. The associations among self-awareness, emotional well-being, and employment outcome following acquired brain injury: A 12-month longitudinal study. *Rehabilitation Psychology*. 2006;51(1):50-59.

Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: Relationship to brain damage and outcome. *J Neurotrauma*. 2004;21:1553-1561.

Pike, B., Isbee, M, Atticks, A, and Roos, B. The Use of SCATBI Today. 2006.
Ref Type: Personal Communication

Ponsford JL, Olver JH, Curran C, Ng K. Prediction of employment status 2 years after traumatic brain injury. *Brain Inj*. 1995;9:11-20.

Ponsford J, Willmott C, Rothwell A, Cameron P, Kelly AM, Nelms R, et al. Factors influencing outcome following mild traumatic brain injury in adults. *J Intl Neuropsychol Soc.* 2000;6(5):568-579.

Proctor SP, Dutille KE, Rosenman ES, Zimelman A, Ness J, Reeves D and Elsmore T. Deployment health research study: computer assisted assessment of cognitive performance among Army National Guard members. *Platform presentation at the Sixth Annual Force Health Protection Conference.* 2003

Proctor SP, Dutille KE, Rosenman, ES, Ness J and Reeves DL. Computer-based assessment of cognitive abilities in a deployment health research study of us Army Nation Guard members. *Platform presentation at the International Applies Military Workshop "From Computer-based Assessment to Augmented Cognition: Improving the Use of Computers from Selection to Operational Environment" hosted by the Autrian Ministry of Defense,* Vienna, Austria. 2002.

Rees P. Contemporary Issues in Mild Traumatic Brain Injury *Arch Phys Med Rehabil.* 2003;84:1885-1894.

Reeves D, Kane R, Winter K, Goldstone A. (1995). Automated Neuropsychological Assessment Metrics (ANAM V3.11): Clinical and Neurotoxicology subsets. Technical Report: National Cognitive Recovery Foundation NCRF-SR-95-01

Riemann BL and Guskiewicz KM. Effects of Mild Head Injury on Postural Stability as Measured Through Clinical Balance Testing. *J Athl Train* 2000;35:19-25.

Reitan RM, Wolfson D. The two faces of mild injury. *Arch Clin Neuropsychol*. 1999;14:191-202.

Riemann BL, Guskiewicz KM. Effects of mild head injury on postural stability as measured through clinical balance testing. *J Athl Train.* 2000;35:19-25.*

Rimel RW, Giordani B, Barth JT, Boll TJ, Jane JA. Disability caused by minor head injury. *Neurosurgery.* 1981;9(3):221-228.

Ropper AH, Gorson KC. Concussion. *N Engl J Med*. 2007;356:166-172.

Rothoerl RD, Woertgen C, Holzschuh M, Metz C, Brawanski A. S-100 serum levels after minor and major head injury. *J Trauma*. 1998;45;765-767.*

Rubin AM, Woolley SM, Dailey VM, Goebel JA. Postural stability following mild head or whiplash injuries. *Am J Otol.* 1995;16:216-221.*

Ruff RM, Jurica P. In search of a unified definition for mild traumatic brain injury. *Brain Inj.* 1999;13(12):943-952.

Ruff R, Marshall L, Crouch M, Klauber M, Levin S, Barth J, et. al. Predictors of outcome following severe head trauma: Follow-up data from the Traumatic Coma Data Bank. *Brain Inj*. 1993;7:101-111.

Ruffolo CF, Friedland JF, Dawson DR, Colantonio A, Lindsay PH. Mild traumatic brain injury from motor vehicle accidents: Factors associated with return to work. *Arch Phys Med Rehabil.* 1999;80(4):392-398.

Ryan L, French L. (2006) TBI During Wartime: The Iraq and Afghanistan Experience. Presented at the 2nd Federal Interagency Conference on Traumatic Brain Injury: Integrating Models of Research and Service Delivery, Bethesda Maryland.

Ryan TV, Sautter SW, Capps CF, Meneese W, Barth JT. Utilizing neuropsychological measures to predict vocational outcome in a head trauma population. *Brain Injury.* 1992;6(2):175-182.

Sabatini AM. Analysis of postural sway using entropy measures of signal complexity. *Med Biol Eng Comput.* 2000;38:617-624.

Sadowski-Cron C, Schneider J, Senn P, Radanov BP, Ballinari P, Zimmerman H. Patients with mild traumatic brain injury: Immediate and long-term outcome compared to intra-cranial injuries on CT scan. *Brain Inj*. 2006;20:1131-1137.

Salazar AM, Warden DL, Schwab K, Spector J, Braverman S, Walter J, et al. Cognitive rehabilitation for traumatic brain injury: A randomized trial. Defense and Veterans Head Injury Program (DVHIP) Study Group. *JAMA* 2000;283(23):3075-3081.

Schoenhuber R, Gentilini M. Anxiety and depression after mild head injury: Case control study. *J Neurol Neurosurg Psychiatry.* 1988;51(5):722-724.

Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry*. 2003;15:341-349.

Sheedy J, Geffen G, Donnelly J, Faux S. Emergency department assessment of mild traumatic brain injury and prediction of post-concussive symptoms at one month post injury. *J Clin Exp Neuropsychol*. 2006;28:755-772.

Sherer M, Bergloff P, High W, Nick T. Contribution of functional ratings to prediction of long term employment outcome after traumatic brain injury. *Brain Inj*. 1999;13:973-981.

Sherer M, Novack TA, Sander AM, Struchen MA, Alderson A, Thompson RN. Neuropsychological assessment and employment outcome after traumatic brain injury: A review. *The Clinical Neuropsychologist*. 2002;16(2):157-178.

Smith-Seemiller L, Fow NR, Kant R, Franzen MD. Presence of post-concussion syndrome symptoms in patients with chronic pain vs. mild traumatic brain injury. *Brain Inj*. 2003;17:199-206.

Sojka P, Stalnacke B, Bjornstig U, Karlsson J. One-year follow-up of patients with mild traumatic brain injury: Occurrence of post-traumatic stress-related symptoms at follow-up and serum levels of cortisol, S-100B and neuro-specific enolase in acute phase. *Brain Inj*. 2006;20(6):613-620.*

Sosin DM, Sniezek JE, Thurman DJ. Incidence of mild and moderate brain injury in the United States, 1991. *Brain Inj*. 1996;10:47-54.

Stalnacke BM, Bjornstig U, Karlsson K, Sojka P. One-year follow-up of mild traumatic brain injury: post-concussion symptoms, disabilities and life satisfaction in relation to serum levels of S-100B and neurone-specific enolase in acute phase. *J Rehabil Med*. 2005;37:300-305.

Stapert S, Houx P, de Kruijk J, Ponds R, Jolles J. Neurocognitive fitness in the sub-acute stage after mild TBI: The effect of age. *Brain Inj*. 2006;20:161-165.

Stapert S, de Kruijk J, Houx P, Menheere P, Twijnstra A, Jolles J. S-100B concentration is not related to neurocognitive performance in the first month after mild traumatic brain injury. *Eur Neurol*. 2005;53:22-26.*

Sterr A, Herron KA, Hayward C, Montaldi D. Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussive syndrome. *BMC Neurology*. 2006;6:7.

Stranjalis G, Korfias S, Papapetrou C, Kouyialis A, Boviatsis E, Psachoulia C. Elevated serum S-100B protein as a predictor of failure to short-term return to work or activities after mild head injury. *J Neurotrauma.* 2004 Aug;21(8):1070-5.

Stulemeijer M, van der Werf SP, Jacobs B, Biert J, van Vugt AB, Brauer JM, Vos PE. Impact of additional extracranial injuries on outcome after mild traumatic brain injury. *J Neurotrauma*. 2006;23:1561-1569.

Susco TM, Valovich McLeod TC, Gansneder BM, Shultz SJ. Balance recovers within 20 minutes after exertion as measured by the balance error scoring system. *J Athl Train.* 2004;39:241-246.

Thurman DJ, Alverson C, Dunn KA, Guerreero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. *J Head Trauma Rehabil.* 1999;14(6):602-615.

Townend W, Dibble C, Abid K, Vail A, Sherwood R, Lecky F. Rapid elimination of protein S-100B from serum after minor head trauma. *J Neurotrauma.* 2006 Feb;23(2):149-55.

Townend W, Guy M, Pani M, Martin B, Yates D. Head injury outcome prediction in the emergency department: A role for protein S-100B. *J Neurol Neurosurg Psychiatry*, 2002;73:542-546.

Valovich TC. *The use of the standardized assessment of concussion and balance error scoring system and learning effects in youth sports participants* [dissertation]. Charlottesville, VA: University of Virginia; 2002.

Van der Naalt J, Van Zomeren AH, Sluiter WJ, Minderhoud JM. Acute behavioural disturbances related to imaging studies and outcomes in mild-to-moderate head injury. *Brain Inj*. 2000;14(9):781-788.

Vanderploeg, R. D., Curtiss, G., Belanger, H. G. Long-term neuropsychological outcomes following mild traumatic brain injury. *J Intl Neuropsychol Soc.* 2005;11:228-236. *

Veltman RH, VanDongen S, Jones S, Buechler CM, Blostein P. Cognitive screening in mild brain injury. *J Neurosci Nurs.* 1993;25(6):367-371.

Vos PE, Lamers KJ, Hendriks JC, van Haaren M, Beems T, Zimmerman C, et al. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. *Neurology*. 2004;62:1303-1310.

Wade LD, Canning CG, Fowler V, Felmingham KL, Baguley IJ. Changes in postural sway and performance of functional tasks during rehabilitation after traumatic brain injury. *Arch Phys Med Rehabil.* 1997;78:1107-1111.

Walker W, Seel R, Curtiss G, Wardent D. Headache after moderate and severe traumatic brain injury: A longitudinal analysis. *Arch Phys Med Rehabil.* 2005;86(9):1793-1800.

Warden D, et al. War neurotrauma: The defense and veterans brain injury center (DVBIC) experience at Walter Reed Army Medical Center (WRAMC). *J Neurotrauma*. 2005;22 (10): 1178.

Waterloo K, Ingebrigtsen T, Romner B. Neuropsychological function in patients with increased serum levels of protein S-100 after minor head injury. *Acta Neurochir (Wien).* 1997;139:26-32.*

Wiesmann M, Missler U, Gottman D, Gehring S. Plasma s-100b protein concentration in healthy adults is age and sex independent. *Clin Chem.* 1998;44:1056-1058.

Wilberger J, Deeb Z, Rothfus W. Magnetic resonance imaging in cases of severe head injury. *Neurosurgery.* 1987;20:571-576.

Wilkins JC, Valovich McLeod TC, Perrin DH, Gansneder BM. Performance on the balance error scoring system decreases after fatigue. *J Athl Train.* 2004;39:156-161.

Wood RL, Yurdakul LK. Change in relationship status following traumatic brain injury. *Brain Injury*. 1997 Jul;11(7):491-501.

Zahra SN, Weinhofer A, Sarahrudi K, Heinz T, Vescei V. Predictive value of S-100B protein and neuron specific-enolase as markers of traumatic brain damage in clinical use. *Brain Inj*. 2006;20(5):463-468.

* References that were reviewed but not cited

APPENDICES

Appendix A – Abstracts Presented
Appendix B – Research Staff Listing
Appendix C – Data Collection Forms
Appendix D – Support Data

APPENDIX A

ABSTRACT PRESENTED

Department of Defense Military Health Research Forum, San Juan Puerto Rico, April 2004

SERIAL ASSESSMENT OF MILD HEAD INJURY: EARLY PREDICTORS OF OUTCOME

Dischinger PC, Cooper C, Mackenzie CF, Romani W, Spector J

BACKGROUND/PURPOSE: The goal of this research endeavor is to identify a cohort of patients with mild TBI (traumatic brain injury) and follow them for a period of one year (1) to determine injury outcomes and (2) to identify those factors that best predict those patients with long-term sequelae.
METHODS: Identify 300 patients with a mild TBI and obtain baseline measures including biochemical markers, balance measures, clinical findings and neurometric tests. Subjects will be followed at 3-5 days, 7-10 days, 3-, 6-, and 12-months post injury.
RESULTS: We have only just begun patient recruitment and therefore have no results yet. By April, we should have preliminary findings available.
CONCLUSIONS: The anticipated result is that biochemical and/or balance measures will add prognostic power to the prediction of long-term outcomes, and thus, could be used in the field to determine the disposition of soldiers who incur mild traumatic brain injury.

APPENDIX A

ABSTRACT PRESENTED

Annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

THE RELATIONSHIP BETWEEN S100B PROTEIN AND NEUROPSYCHOLOGICAL PERFORMANCE IN MILD TRAUMATIC BRAIN INJURY

Lee-Wilk, T., Dischinger, P., Mackenzie, C., Murdock, K., Imle, P., Spector, J., Kufera, J., Auman, K., Thysen, J.A., and Kane, R.L.

OBJECTIVE: To assess the relationship between S100B protein (a biological serum marker of astroglial cell death representative of CNS damage) and measures of neuropsychological functioning in a sample of participants with mild traumatic brain injury (mTBI).
PARTICIPANTS AND METHODS: Thirty-four participants, ages 18-64, with mTBI (Glasgow Coma Scale 13-15) admitted to an emergency room of an urban hospital were included in this longitudinal study. S100B protein was measured by blood draw upon admission, within 3-10 hours post-injury. Participants were subsequently assessed (within 7-10 days of injury) with the Automated Neuropsychological Assessment Metrics (ANAM), a computerized library of tests designed to serially assess neuropsychological functioning. To reduce the number of variables, several test measures were combined into a weighted composite. In addition, we also included measures of simple (sRT) and choice (pRT) reaction time.
RESULTS: Results of regression analyses adjusted for age, gender, and education indicated a significant relationship between S100 and sRT ($F=9.51$, $p=0.004$). There was no significant relationship between S100B and either the composite score ($F=0.49$, $p=0.488$) or pRT ($F=0.79$, $p=0.381$).
CONCLUSION: Our findings indicated a significant association between S100B protein and sRT. This finding is of interest since sRT is emerging in the literature as a sensitive measure to the effects of concussion. Findings from previous research have been mixed with studies finding and failing to find relations between S100B and performance on cognitive tests. In this analysis of data from our study, S100B was related to reaction time but not to more complex cognitive tasks.

APPENDIX A

ABSTRACT PRESENTED

Annual meeting of the International Neuropsychological Society, Boston, MA, February, 2006.

THE RELATIONSHIP BETWEEN S100B PROTEIN LEVELS AND EFFORT IN MILD TRAUMATIC BRAIN INJURY

Thysen, J.A. Lee-Wilk, T., Mackenzie, C., Kane, R.L., Spector, J., Auman, K., Kufera, J., Murdock, K., Imle, P., and Dischinger, P.

OBJECTIVE: To assess the relationship between S100B protein (a biological marker of astroglial cell death representative of CNS damage) and the Word Memory Test (WMT), a test of effort and motivation, in a sample of participants with mild traumatic brain injury (mTBI). The WMT is viewed as a test more sensitive to effort than to brain injury. We hypothesized there would be no relationship between S100B and WMT performance.
PARTICIPANTS AND METHODS: Thirty-four participants admitted to an ER of an urban hospital, ages 18-64, with Glasgow Coma Scales between 13-15, participated in this longitudinal investigation. S100B protein was measured upon admission, within 3-10 hours post-injury. Each participant was administered the WMT 7-10 days following the injury. Repeat WMT data were also available for 32 participants 3 months post injury.
RESULTS: At 7-10 days, 7 participants (18%) failed the Immediate Recall trial (IR) and two participants (5%) failed the Delayed Recall trial (DR) of the WMT. These same two individuals also failed the IR condition. At 3 months, 1 individual failed IR and none failed DR. Results of regression analyses indicated no relationship between S100B protein levels and performance on WMT performance at both one week and three months.
CONCLUSION: No relationship was demonstrated between a biological maker of brain injury (S100B) and WMT performance. A 5% failure rate on both IR and DR was observed at one week. No participant failed both IR and DR at 3 months.

APPENDIX A

ABSTRACT PRESENTED
Department of Defense Military Health Research Forum, San Juan Puerto Rico, May 2006

MILD TRAUMATIC BRAIN INJURY: PREDICTORS OF LONG-TERM OUTCOMES

Patricia C. Dischinger, PhD

BACKGROUND: Each year approximately 1.5 million Americans sustain a traumatic brain injury (TBI), the majority of which are mild. **PURPOSE:** The goal of this research is to determine possible predictors of outcome among a population of patients admitted to a Level I trauma center with mild TBI, defined as either a GCS 13-15, transient loss of consciousness/confusion. **METHODS:** Three major types of tests are conducted at baseline: neurometric tests (The Automated Neuropsychological Assessment Metric Readiness Evaluation System {ARES}, which measures simple and choice reaction time, divided attention of visual and spatial skills, running memory and executive reasoning) , a biochemical marker (S-100 B) and balance measures (Neurocom Balance Master and Balance Error Scoring System{BESS}). In addition, patients are administered the Concussion Symptom Checklist (including symptoms such as headache, irritability, lack of concentration), and the General Well-being Scale. At the 5 follow-up visits (3-5 days, 7-10 days, 3 months, 6 months, and one year post-injury), further neuropsychological tests and balance tests are conducted as well as repeated documentation of symptoms. Subjects are encouraged to return to the hospital for these follow-up visits; however, for those unable to return, documentation of symptoms is obtained by telephone interview. Due to the high prevalence of associated orthopedic injuries, baseline balance testing has been lower than originally anticipated. Therefore, further findings are based on preliminary analyses of neuropsychological and S-100 B tests relative to symptoms reported at the 3 month follow-up**.** **RESULTS:** To date, 130 patients have been enrolled; baseline data are currently available for 108, (59 have completed 3-month evaluations). Subject demographics are as follows: mean age: 34 years, 59% male, 46% high school education or less, and 81% employed. Following injury, the number of symptoms reported increased dramatically; 26% reported $\geq$ 4 symptoms at baseline (previous to the injury); at 3-5 days, this rate increased to 73%, declining to 39% by three months. Symptoms with the highest prevalence at 3-5 days included fatigue (86%), headache (62%), and dizziness (54%). At the three month follow-up, the proportion of subjects with physical symptoms had returned to baseline levels, whereas emotional and cognitive symptoms remained elevated. Significant predictors of symptomatology 3 months after injury include increasing age and female gender. Tests of simple reaction time at 7-10 days post-injury also predicted symptoms and general well-being at 3 months. No positive association was noted between the S-100 B findings and symptoms at 3 months; in fact, for the subgroup analyzed to date, those with lower S-100 B levels reported more symptoms than those with higher levels. For subjects with less than 4 symptoms at 3 months, the median S-100 B was 0.036µg/L, in contrast to 0.016µg/L for those with more symptoms. **CONCLUSION:** Several demographic factors (age and sex) and simple reaction time at 7-10 days post-injury were found to be significant predictors of post-concussive symptoms at 3 months. However, S-100 B levels were inversely associated with the number of symptoms at 3 months. Six and twelve month evaluations continue and analyses are ongoing.

APPENDIX A

ABSTRACT PRESENTED

American Psychiatric Association Annual Meeting, Toronto, Canada, May 2006

THE EFFECTS OF DEPRESSION AND ANXIETY ON NEUROPSYCHOLOGICAL PERFORMANCE IN MILD TRAUMATIC BRAIN INJURY

Lee-Wilk, Terry; Kane, Robert L.; Mackenzie, Colin; Spector, Jack, Murdock, Karen; Kufera, Joseph; Auman, Kimberly; Imle, Portia; Thysen, Julie; Lonser, Kara; Dischinger, Patricia

OBJECTIVE: To assess performance on measures of neuropsychological functioning in a sample of participants with mild traumatic brain injury (mTBI) with and without co-morbid mood or anxiety symptoms.
METHODS: Forty-six participants, ages 18-64, with mTBI (Glasgow Coma Scale 13-15) admitted to an emergency room of an urban hospital were included in this longitudinal study. Participants were asked to report anxiety and depression symptoms as part of a clinical interview 3 months post injury. Participants were also assessed with the Automated Neuropsychological Assessment Metrics (ANAM), a computerized library of tests designed to serially assess neuropsychological functioning. Groups were divided into those with or without depression/anxiety symptoms. To reduce the number of variables, several tests were combined into a weighted composite. In addition, measures of simple (sRT) and choice (pRT) reaction time were measured.
RESULTS: Results of regression analyses adjusted for age, gender, education, and S100B (a biological serum marker of astroglial cell death representative of CNS damage) indicated no difference between 1) those with or without symptoms of *depression* on the three outcomes (p=0.44-0.66); 2) those with or without symptoms of *anxiety* on the three outcomes (p=0.37-0.44); 3) those with or without symptoms of *depression or anxiety* on the three outcomes (p=0.40-0.48).
CONCLUSIONS: Findings from previous literature have consistently documented the association between mild TBI and symptoms of depression and anxiety. However, the literature is mixed regarding the effects of depression and anxiety on performance on neuropsychological measures in mild TBI samples. These findings suggest no group differences on measures of sRT, pRT, or overall neuropsychological functioning. Although depression and anxiety may be common in mild head injury, it does not mediate deficits observed on measures of neuropsychological functioning in this sample.

APPENDIX A

ABSTRACT PRESENTED

American Association for the Surgery of Trauma (AAST) 65th Annual Meeting, New Orleans, LA, September, 2006

PREDICTORS OF POST-CONCUSSIVE SYMPTOMS AT THREE MONTHS

Gabriel E. Ryb, Carnell Cooper, Patricia C. Dischinger, Kimberly M. Auman, Robert L. Kane, Terry Lee-Wilk, Karen Murdock, Cris Imle

OBJECTIVE: to determine predictors of outcome among patients with mild traumatic brain injury (TBI).
METHODS: subjects with either a GCS 13-15, transient loss of consciousness or confusion, and normal brain CTs were recruited at a level I trauma center. S-100 B levels and the concussion symptom checklist were obtained on admission. Symptoms were reassessed at 3-5 days and at 3 months. Symptoms were classified as physical (headaches, dizziness, double vision, fatigue, photophobia and noise sensitivity), cognitive (concentration, memory and thinking difficulties) and emotional (anxiety, depression and irritability). The outcome studied was the number of symptoms at 3 months. Linear regression models (α=0.05) including S-100B, age, gender, education, ISS, previous TBI, and baseline and initial symptoms were built.
RESULTS: Data were available for 108 patients with 59 completing 3-month evaluations. Subjects were on average 34 years old, 54% male and 37% had $\leq$ 12 years of education. Following injury, the percentage of cases reporting $\geq$ 4 symptoms increased from 26% pre-injury to 73% at 3-5 days, declining to 39% by the third month. Physical symptoms were present in 95% of the patients at 3-5 days. At the three month follow-up the proportion of subjects with physical symptoms had returned to pre-injury levels. Emotional and cognitive symptoms remained elevated (35% and 37% at baseline, 53% and 66% at 3-5 days, and 51% and 61% at 3 months respectively). Predictors of increased symptomatology at 3 months included older age, female gender, higher educational achievement, and previous TBI. Pre injury and initial symptoms, ISS, and elevated S-100 B did not predict 3 months increased symptomatology.
CONCLUSION: Initial symptoms and elevated S-100 B levels do not predict post-concussive symptoms at 3 months. Older age, female gender, higher educational achievement and history of previous TBI, however, were found to be significant predictors of outcome among mild TBI patients. While physical symptoms are more commonly reported initially, cognitive and emotional symptoms are more likely to persist for 3 months.

APPENDIX A

ABSTRACT PRESENTED

Annual Meeting of the International Neuropsychological Society, Portland, OR, February 2007

EFFECTS OF OVERALL INJURY SEVERITY ON ANAM PERFORMANCE IN MILD TRAUMATIC BRAIN INJURY

Bercaw, E. L., Kane, R. L., Kufera, J., Auman, K., Murdock, K., Lee-Wilk, T., Imle, P., Dischinger, P., Mackenzie, C., Cernich, A. N., Stern, S., & Wulff, L. L.

ABSTRACT: Patients with mild traumatic brain injury (mTBI; GCS 13-15) were recruited from an urban trauma center to investigate functional and cognitive outcomes following mTBI and to relate cognitive performance to the persistence of posttraumatic symptoms and functional status at 6 and 12 months post-injury. At 6 months, age of participants (N=53) was 18-60 (M=36.45, SD=12.8), and 58% of the sample was male. The Automated Neuropsychological Assessment Metrics (ANAM), a brief computerized battery of neurocognitive measures useful in the assessment of neuropsychological effects of concussion, was used to track neurocognitive function at different time points post injury. While brain injuries were mild according to criterion, many participants sustained trauma to multiple areas of the body which could indirectly affect performance on neurocognitive measures. The goal of the present analysis was to establish the degree to which non-brain related physical injury, assessed by total Injury Severity Scale (ISS), impacted ANAM performance at 7-10 days and 6-months post-injury. Results indicated that moderate and severe injury (ISS 9-16 and >16, respectively) were associated with increased simple reaction time at 6 months when controlling for age, education, previous mTBI, and history of ADHD or learning disability ($p<.05$). However, ISS was not associated with performance on a complex reaction time test or on an overall index score reflecting performance efficiency on more cognitively demanding tasks. Findings demonstrated that the extent of physical injury did not impact overall neurocognitive test performance but did impact simple reaction time, a measure commonly used to assess cognitive status post mTBI.

APPENDIX B

Research Staff – Complete Listing		
Personnel	***Department***	***Dates of Service***
Aarabi, Bizhan	Neurosurgery	7/2003 – 4/2006
Alexander, Melvin	National Study Center	7/2004, 3 - 6/2005
Alvarez, Elizabeth	UMMC, Physical Therapy	7/2003 – 11/2004
Asher, Yifaat	UMMC, Speech Language Pathology	7/2006 – 1/2007
Atticks, Andrea	UMMC, Speech Language Pathology	9/2004 – 12/2005
Auman, Kimberly M. **	National Study Center	4/2003 – 3/2007
Bercaw, Edwin	VA, Neuropsychology	7/2006 – 3/2007
Cernich, Alison	VA, Neuropsychology	7/2005 – 3/2007
Cooper, Carnell **	Surgery	7/2003 - 4/2006
Dischinger, Patricia C. **	National Study Center	4/2003 – 3/2007
Fortson, Angelique	National Study Center	10/2006 – 3/2007
Gemmell, Leigh	National Study Center	4/2006
Hall, Linda	UMMC, Speech Language Pathology	7/2003 – 12/2005
Harris, Diane	National Study Center	3/2004 – 3/2006
Hsu, Nancy	VA, Neuropsychology	7/2004 – 6/2005
Imle, P. Cristine	National Study Center	7/2003 – 3/2007
Isbee, Malka	UMMC, Speech Language Pathology	9/2004 – 1/2007
Jones, Amy	National Study Center	7/2003 – 1/2007
Kane, Robert **	VA, Neuropsychology	11/2004 – 3/2007
Kufera, Joseph A. **	National Study Center	4/2003 – 3/2007
Lee-Wilk, Terry	VA, Neuropsychology; NSC	9/2003 – 3/2007
Logan, Jennifer	UMMC, Physical Therapy	7/2003 – 11/2004
London, Erika	National Study Center	5/2004 – 9/2004
Mackenzie, Colin **	National Study Center	4/2003 – 3/2007
Murdock, Karen R. **	National Study Center	6/2003 – 3/2007
Nolan Cunningham, Amy	National Study Center	2/2005 – 8/2005
OConnor, James	Trauma Surgery	7/2003 – 4/2006
Okupniarek, Jennifer	UMMC, Speech Language Pathology	1/2004 – 11/2004
Pike, Bonnie	UMMC, Speech Language Pathology	7/2003 – 1/2007
Romani, William **	UMB, Physical Therapy	4/2003 – 3/2007
Roos, Brianne	UMMC, Speech Language Pathology	4/2005 – 12/2006
Ryan, Gregory	VA, Neuropsychology	7/2004 – 6/2005
Ryb, Gabriel **	Trauma Surgery, National Study Center	7/2006 – 3/2007
Spector, Jack	National Study Center	12/2003 – 12/2004
Stern, Susan	National Study Center	8/2006 – 9/2006
Thysen, Julie	VA, Neuropsychology	7/2005 – 6/2006
Volpini, Karen	National Study Center	12/2003 – 9/2006
Wulff, Laura	VA, Neuropsychology	7/2006 – 1/2007
***** Staff with continued role in data analysis and dissemination through March 2008***		

APPENDIX C – SELECTED DATA COLLECTION FORMS

C-1 **Initial Interview**

C-2 **3-5 and 7-10 Day Interview**

C-3 **3, 6 and 12 Month Interview**

C-4 **GOAT**

C-5 **Symptom Checklist**

C-6 **Well-Being Scale**

C-7 **BESS**

APPENDIX C-1

A Multidisciplinary Evaluation of Mild TBI: Early Predictors of Outcome - Initial Assessment

Study ID #: __ __ __
Interview Date: __ __/ __ __ /__ __
Interviewers ID: __ __ __

This form is to be completed for all subjects enrolled in the mild TBI Project. Begin the interview by verifying the type of incident that lead to the patient being admitted to the Shock Trauma Center. This page is **not** to be entered in the database. This form is to be returned to the Coordinating Office at the National Study Center within 24 hours of completion. Please remind the subject that he/she has the right to refuse to answer any item without impact (repercussion) on his/her care.

Current Injury Information:

Mr/Mrs/Ms _____ it is my understanding that you were admitted to the STC on __ __/__ __/__ __ because you were involved in a

☐ 1. Motor Vehicle Crash ☐ 2. Motorcycle Crash ☐ 3. Fall
☐ 4. Pedestrian Collision ☐ 5. Beating / Fight ☐ 6. Other _____

Is this correct? ☐ 1. Yes ☐ 2. No ☐ 8. Refused

If the information is incorrect, please provide the correct information in the space provided.

Name: _____ _____ _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Locator Information:

1. Name: _____ _____ _____ Relationship: _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip
Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

1. Name: _____ _____ _____ Relationship: _____
First Middle Last
Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip
Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Injury Information:

1. Admit Date: ___ ___/___ ___/___ ___
2. Injury Date: ___ ___/___ ___/___ ___
3. Mini-Mental Score: ___ ___
4. Admission GCS: ___ ___
5. GOAT: ___ ___

Demographic Information:

1. Sex: ☐ 1. Male ☐ 2. Female
2. Age: ___ ___ years
3. Do you consider yourself to be Hispanic? : ☐ 1. Hispanic ☐ 2. Non-hispanic
4. What race do you consider yourself to be? (Check all that apply):

1) ☐ White
2) ☐ African American
3) ☐ Native American / Alaska Native
4) ☐ Pacific Islander/ Native Hawaiian
5) ☐ Asian
6) ☐ Other: _____

5. Marital Status:

1) ☐ Single
2) ☐ Married
3) ☐ Living as married
4) ☐ Separated
5) ☐ Divorced
6) ☐ Widowed
7) ☐ Unknown

6. What is the highest grade or year of school you have completed?

1) ☐ Eighth grade or less
2) ☐ Some high school
3) ☐ High school graduate or GED certificate
4) ☐ Some technical school
5) ☐ Technical school graduate
6) ☐ Some college
7) ☐ College graduate - Associates
8) ☐ College graduate - Bachelors
9) ☐ Post graduate or professional degree - Masters
10) ☐ Post graduate or professional degree - Doctorate
11) ☐ Post graduate or professional degree - Medical
12) ☐ Post graduate or professional degree - Other: _____

7. Who do you live with?

1) ☐ Alone
2) ☐ Spouse
3) ☐ Parents
4) ☐ Child < 21
5) ☐ Child ≥ 21 / other relative
6) ☐ Roommate
7) ☐ Other: _____
8) ☐ Spouse and other family _____

8. Employment:

If subject is employed full-time and going to school part-time select Employed, Full-time.
If subject is student full-time and working part-time select Student, Full-time

1) ☐ Employed, Full-time (including self employment) Title: _____
2) ☐ Employed, Part-time (including self employment) Title: _____
3) ☐ Student, Full -time
4) ☐ Student, Part-time
5) ☐ Homemaker
6) ☐ Out of work / Unemployed
7) ☐ Other: _____ (Note if not working due to disability)

Medical History:

9. Did you have a period of loss of consciousness or amnesia to event? ☐ 1. Yes ☐ 2. No
10. How long? ___ ___ minutes
11. Did you have any nausea or vomiting associated with this injury:

1) Nausea ☐ 1. Yes ☐ 2. No
2) Vomiting ☐ 1. Yes ☐ 2. No

12. We are interested in finding out about any past injuries you may have had. Please tell me, in the last year, have you required medical attention in a doctor's office, an emergency department or have you been hospitalized for an injury (ie.) related to car crash, motorcycle crash, being hit by car, a fall or a recreational mishap (ie. hurt while playing sports), assaulted or being in a fight? ☐ 1. Yes ☐ 2. No

13. Prior to this injury had you been diagnosed with any of the following conditions?

		1. Yes	2. No	
1)	Previous Brain Injury/Concussion	☐	☐	Describe: _____
2)	Attention Deficit Disorder	☐	☐	Describe: _____
3)	Learning Disability	☐	☐	Describe: _____
4)	Anxiety Disorder	☐	☐	Describe: _____

		1. Yes	2. No	
5)	Motion Sickness	☐	☐	Describe: _____
6)	Vertigo	☐	☐	Describe: _____
7)	Depression	☐	☐	Describe: _____
8)	Seizure disorder or epilepsy	☐	☐	Describe: _____
9)	Glasses or contacts	☐	☐	Describe: _____
10)	Hearing Loss	☐	☐	Describe: _____

14. Prior to your injury did you have any of the following medical (physical) conditions? If yes were you taking medications for these conditions?

		Condition		Medication	
		1. Yes	2. No	1. Yes	2. No
1)	Pregnant (currently)	☐	☐	☐	☐
2)	Hypertension	☐	☐	☐	☐
3)	Heart Disease	☐	☐	☐	☐
4)	Diabetes	☐	☐	☐	☐
5)	Cancer	☐	☐	☐	☐
6)	Mood Disorder	☐	☐	☐	☐
7)	Psychiatric disorder	☐	☐	☐	☐
8)	Glaucoma	☐	☐	☐	☐
9)	Macular Degeneration	☐	☐	☐	☐

15. Prior to your injury did you have any problems with your balance? 1. Yes ☐ 2. No ☐

Describe:_____

16. Have you ever needed special education or other services due to learning difficulties? 1. Yes ☐ 2. No ☐

Describe:_____

17. Prior to your injury did you ever use an assistive device (cane, crutch) to walk? 1. Yes ☐ 2. No ☐

How often? When?:_____

18. Current Medication Use (including Prescription, Over-the-counter medications, vitamins, supplements)

	Prior to injury	Since admit
1	_____	_____
2	_____	_____
3	_____	_____
4	_____	_____
5	_____	_____
6	_____	_____
7	_____	_____

19. How often do you have a drink Containing Alcohol? (Skip to 24 if answers "never")

1. ☐ Never
2. ☐ Monthly or less
3. ☐ Two to four times a month
4. ☐ Two to three times a week
5. ☐ Four or more times a week
8 ☐ Refused

		1. Yes	2. No	
20.	Have you ever felt you should cut down on your drinking?	☐	☐	
21.	Have people annoyed you by criticizing your drinking?	☐	☐	
22.	Have you ever felt bad or guilty about your drinking?	☐	☐	
23.	Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)?	☐	☐	
24.	Do you currently use illicit (street) drugs?	☐	☐	If no, skip to 24

(Including: Cocaine/crack, Marijuana/pot, Stimulants/uppers, LSD/mescaline, Tranquillizers, Pain Killers, Heroin/opiates, PCP, Sniff gases or fumes, Ectasy, etc)

		1. Yes	2. No
1.	Have you ever felt you should cut down on your drug use?	☐	☐
2.	Have people annoyed you by criticizing your drug use?	☐	☐
3.	Have you ever felt bad or guilty about your drug use?	☐	☐
4.	Have you ever used drugs the first thing in the morning to get going or treat withdrawal symptoms		
5.	(eye-opener)?	☐	☐

25. During the past month, have you often been bothered by feeling down, depressed or hopeless?
☐ 1. Yes ☐ 2. No
26. During the past month, have you often been bothered by little interest or pleasure in doing things?
☐ 1. Yes ☐ 2. No
27. Do you have a latex allergy?
☐ 1. Yes ☐ 2. No
28. Do you have Advanced Directives?
☐ 1. Yes ☐ 2. No If yes, request a copy for files and note at each eval

There are many factors that may influence the results of today's tests; therefore we are asking the following questions of everyone.

Code as: *1=1-12 hours 2=13-24 hours 3=25-48 hours 4=>48 hours 5=does not use*

29. When did you last have anything containing

Caffeine	Date_____	Time_____	_____
Alcohol	Date _____	Time_____	_____
"Street drugs"	Date_____	Time_____	_____

Comments:_____

_____

_____

_____

_____

APPENDIX C-2

A Multidisciplinary Evaluation of Mild TBI: Early Predictors of Outcome - 3-5, 7-10 Day Follow-up

Study ID #: __ __ __

Interview Date: __ __/ __ __ / __ __

Interviewers ID: __ __ __

This form is to be completed for all subjects returning for their 3 to 5 day follow-up. The completed form is to be returned to the Coordinating Office at the NSC within 24 hours of completion.

Please remind the subject that he/she has the right to refuse to answer any item without impact (repercussion) on his/her care.

Contact Information:

Are there any changes?

Name: _____ _____ _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Locator Information:

1. Name: _____ _____ _____ Relationship: _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

1. Name: _____ _____ _____ Relationship: _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Medication Use

Current Medication Use (including Prescription, Over-the-counter medications, vitamins, supplements)

1)_____

2)_____

3)_____

4)_____

5)_____

6)_____

7)_____

Post-Injury Care

1. Since your discharge from Shock Trauma on __ __/ __ __/ __ __ __ __, have you been seen by a doctor for your injury?

☐ 1. Yes ☐ 2. No

☐ PCP* – Related to TBI ☐ PCP – Related to PMHx ☐ ED visit, no admit

☐ Still STC IP ☐ Multiple appointments(details below)

☐ STC Clinic visit ☐ New injury/accident Other/ describe:

**PCP = Primary Care Provider*

2. Since your discharge from Shock Trauma , have you been referred to any of the following services?

	1. Yes	2. No
1) Physical Therapy	☐	☐
2) Speech Therapy	☐	☐
3) Occupational Therapy	☐	☐
4) Psychological Counseling	☐	☐

3. Have you received any of the following services, related to your injury?

	1. Yes	2. No
10) Physical Therapy	☐	☐
11) Speech Therapy	☐	☐
12) Occupational Therapy	☐	☐
13) Psychological Counseling	☐	☐

4. If you were referred but did not receive the above services, why not?

Did not feel I needed the services	1. ☐
Did not know how to access the services	2. ☐
Insurance would not pay for services	3. ☐
Employer would not pay for services	4. ☐
Unable to pay for services	5. ☐
Other:_____	6. ☐
Missing/ refused	9. ☐

5. Have you been hospitalized for reasons related to your injury?

☐ 1. Yes ☐ 2. No

Describe:

_____

_____

_____

Work / Social Activities

6. Since your discharge from Shock Trauma have you returned to work / school?

☐ 1. Yes ☐ 2. No

If yes, specify

1. ☐ Returned to same job part-time
2. ☐ Returned to same job full-time
3. ☐ Returned to same company but different job
4. ☐ New job
5. ☐ Returned to school part-time
6. ☐ Returned to school full-time
7. ☐ Other:_____

7. Have you engaged a lawyer / legal services as a result of your injuries?

☐ 1. Yes ☐ 2. No

8. In comparison to pre-injury, have your social activities changed?

☐ 1. Stayed the same

☐ 2. Increased

☐ 3. Decreased

9. In comparison to pre-injury, has your alcohol and/or drug use changed?

☐ 1. Stayed the same

☐ 2. Increased

☐ 3. Decreased

There are many factors that may influence the results of today's tests; therefore we are asking the following questions of everyone.

Code as: 1=1-12 hours 2=13-24 hours 3=25-48 hours 4=>48 hours 5=does not use

10. When did you last have anything containing: **Code**

Caffeine	Date_____Time_____	_____
Alcohol	Date _____Time_____	_____
"Street drugs"	Date_____Time_____	_____

11. Are you pregnant? ☐ 1. Yes ☐ 2. No

Comments:_____

_____

_____

_____

_____

APPENDIX C-3

A Multidisciplinary Evaluation of Mild TBI: Early Predictors of Outcome - 3, 6 & 12 Month Follow-up

Study ID #: __ __ __
Interview Date: __ __/ __ __ / __ __
Interviewers ID: __ __ __

This form is to be completed for all subjects returning for their 3 month follow-up. The completed form is to be returned to the Coordinating Office at the NSC within 24 hours of completion.

Please remind the subject that he/she has the right to refuse to answer any item without impact (repercussion) on his/her care.

Contact Information:

Are there any changes?

Name: _____ _____ _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Locator Information:

1. Name: _____ _____ _____ Relationship: _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

1. Name: _____ _____ _____ Relationship: _____
First Middle Last

Street: _____ _____
Street address Apt

_____ _____ _____
City MD Zip

Phone: Home (___) ____ - _____ Pager (___) ____ - _____
Cell (___) ____ - _____ Work (___) ____ - _____

Medication Use

1. Current Medication Use (including Prescription, Over-the-counter medications, vitamins, supplements)

1)_____

2)_____

3)_____

4)_____

5)_____

6)_____

7)_____

Post-Injury Care

2. Since your last visit with us on __ __/__ __/__ __, have you been seen by a doctor about your injury?

☐ 1. Yes ☐ 2. No

☐ PCP* – Related to TBI ☐ PCP – Related to PMHx ☐ ED visit, no admit

☐ Still STC IP ☐ Multiple appointments (details below)

☐ STC Clinic visit ☐ New injury/accident Other/ describe:

**PCP = Primary Care Physician*

3. Since your last visit with us on __ __/__ __/__ __ , have you been referred to any of the following services?

	1. Yes	2. No
1) Physical Therapy	☐	☐
2) Speech Therapy	☐	☐
3) Occupational Therapy	☐	☐
4) Psychological Counseling	☐	☐

4. Have you received any of the following services, related to your injury?

	1. Yes	2. No
1) Physical Therapy	☐	☐
2) Speech Therapy	☐	☐
3) Occupational Therapy	☐	☐
4) Psychological Counseling	☐	☐

5. If you were referred but did not receive the above services, why not?

Did not feel I needed the services	1. ☐
Did not know how to access the services	2. ☐
Insurance would not pay for services	3. ☐
Employer would not pay for services	4. ☐
Unable to pay for services	5. ☐
Other:_____	6. ☐
Missing/ refused	9. ☐

6. Have you been hospitalized for reasons related to your injury?

☐ 1. Yes ☐ 2. No

5.a. Describe:

_____

_____

_____

7. We are interested in finding out about injuries you may have had since your discharge from STC on __ __/__ __/__ __. Please tell me, if you required medical attention in a doctor's office, an emergency department or have you been hospitalized for an injury (ies) related to car crash, motorcycle crash, being hit by car, a fall or a recreational mishap (ie. hurt while playing sports), assaulted or being in a fight?

☐ 1. Yes ☐ 2. No

If yes 6a.	MVA	[1] ☐	Sports injury	[5] ☐
	MCA	[2] ☐	Assault/fight	[6] ☐
	Pedestrian	[3] ☐	GSW	[7] ☐
	Fall	[4] ☐	Missing/refused	[9] ☐

8. Since we last saw you on __ __/__ __/__ __, have you been injured where you bumped your head?

☐ 1. Yes ☐ 2. No If yes, describe:_____

_____

9. During the past month, have you often been bothered by feeling down, depressed or hopeless?

☐ 1. Yes ☐ 2. No

10. During the past month, have you often been bothered by little interest or pleasure in doing things?

☐ 1. Yes ☐ 2. No

11. Since your injury have you been diagnosed with any of the following medical (physical) conditions?

1.	Pregnant	☐ 1. Yes	☐ 2. No
2.	Psychiatric disorder	☐ 1. Yes	☐ 2. No
3.	Depression	☐ 1. Yes	☐ 2. No
4.	Mood disorder	☐ 1. Yes	☐ 2. No
5.	Seizure disorder	☐ 1. Yes	☐ 2. No

a. If Yes, How many seizures in last 3 months?_____

b. Describe,

other:_____

Work / Social Activities

If subject is employed full-time and going to school part-time select: Employed, Full-time
If subject is student full-time and working part-time select: Student, Full-time

12. Since we last saw you on __ __/__ __/__ __, have you returned to work / school?

☐ 1. Yes ☐ 2. No

If yes, specify 11.a.

8. ☐ Returned to same job part-time
9. ☐ Returned to same job full-time
10. ☐ Returned to same company but different job
11. ☐ New job
12. ☐ Returned to school part-time
13. ☐ Returned to school full-time
14. ☐ Other:_____

13. Have you engaged a lawyer / legal services as a result of your injuries?

☐ 1. Yes ☐ 2. No

14. In comparison to pre-injury, have your social activities changed?

☐ 1. Stayed the same
☐ 2. Increased
☐ 3. Decreased

15. In comparison to pre-injury, has your alcohol and/or drug use changed?

- ☐ 1. Stayed the same
- ☐ 2. Increased
- ☐ 3. Decreased

There are many factors that may influence the results of today's tests; therefore we are asking the following questions of everyone.

Code as: 1=1-12 hours 2=13-24 hours 3=25-48 hours 4=>48 hours 5=does not use

15. When did you last have anything containing:		**Code**
Caffeine	Date_____Time_____	_____
Alcohol	Date _____Time_____	_____
"Street drugs"	Date_____Time_____	_____

Comments:_____

_____

_____

_____

_____

APPENDIX C-4
A Multidisciplinary Evaluation of Mild TBI - Galveston Orientation and Amnesia Test (GOAT)

Study ID #: __ __ __
Interview Date: __ __/ __ __ / __ __ __ __
Interviewers ID: __ __ __

This form is to be returned to the Coordinating Office at the National Study Center within 24 hours of completion.

Make sure patient cannot see a calendar/clock or look at his/her watch. Do not allow friends/relatives to coach.

Current time: _____:_____ am/ pm Day of the Week: Su M T W Th F Sa

Error Pts.

1. What is your name? (2)_____When were you born? (4)_____ _____

Where do you live? (4)_____ _____

2. Where are you now (5) City_____ (5) Hospital_____ _____
(unnecessary to state name of hospital)

3. On what date were you admitted to this hospital? (5)_____ _____

How did you get here? (5)_____ _____

4. What is the first event you can remember after the injury? (5)_____ _____

Can you describe in detail (e.g. date, time, companions) the first event you can recall after the injury? (5)

_____ _____

5. Can you describe the last event you recall before the accident/injury? (5)_____ _____

Can you describe in detail (e.g. date, time, companions) the first event you can recall be fore the injury? (5)

_____ _____

6. What time is it now? (-1 for each ½ hour removed from the correct time to maximum of -5)_____ _____

7. What day of the week is it? (-1 for each day removed from correct one to maximum -3) _____ _____

8. What day of the month is it? (-1 for each day removed from correct one to a maximum of -5) _____ _____

9. What is the month? (-5 for each month removed from correct one to maximum of -15) _____ _____

10. What is the year? (-10 for each year removed from correct one to maximum of -30) _____ _____

Total error points _____

Total GOAT score (100 – total error points) _____

76 – 100 = Normal
66 – 75 = Borderline
<65 = Impaired

APPENDIX C-5

A Multidisciplinary Evaluation of Mild TBI: Early Predictors of Outcome - Concussion Symptom Checklist

Study ID#: __ __ __
Interview Date: __ __/ __ __/ __ __
Interviewer's ID#: __ __ ___

Scale for each question 1 to 10 1 = no symptoms (ie headache, irritability) 10 = unbearable symptoms

1. Have you had headaches during the last week? ☐ 1. Yes ☐ 2. (No If No go to 2)
   How many days were you bothered by these headaches during the last week? _____
   How bad are the headaches usually, on a scale from 1 to 10? _____

2. Have you had anxiety during the past week? ☐ 1. Yes ☐ 2. (No If No go to 3)
   How many days were you bothered by this anxiety during the past week? _____
   How bad is the anxiety usually, on a scale from 1 to 10? _____

3. Have you had depression during the last week? ☐ 1. Yes ☐ 2. No (If No go to 4)
   How many days were you bothered by depression during the last week? _____
   How bad is the depression usually, on a scale from 1 to 10? _____

4. Have you had any difficulty concentrating during the last week? ☐ 1. Yes ☐ 2. No (If No go to 5)
   How many days were you bothered by concentration problems during the last week? _____
   How bad is your concentration, on a scale from 1 to 10? _____

5. Have you had dizziness during the last week? ☐ 1. Yes ☐ 2. No (If No go to 6)
   How many days were you bothered by dizziness during the last week? _____
   How bad is the dizziness, on a scale from 1 to 10? _____

6. Have you had trouble remembering things during the last week? ☐ 1. Yes ☐ 2. No (If No go to 7)
   How many days did you have trouble remembering things during the last week? _____
   How bad are the memory problems, on a scale from 1 to 10? _____

7. Have you had blurry or double vision during the last week? ☐ 1. Yes ☐ 2. No(If No go to 8)
   How many days were you bothered by vision problems during the last week? _____
   How bad is the blurry or double vision usually, on a scale from 1 to 10? _____

8. Have you had trouble thinking during the last week? ☐ 1. Yes ☐ 2. No (If No go to 9)
   How many days did you have trouble thinking during the last week? _____
   How bad is the trouble thinking usually, on a scale from 1 to 10? _____

9. Have you been irritable during the past week? ☐ 1. Yes ☐ 2. No (If No go to 10)
   How many days were you irritable during the last week? _____
   How bad is the irritability usually, on a scale from 1 to 10? _____

10. Have you been tired a lot during the past week? ☐ 1. Yes ☐ 2. No (If No go to 11)
    How many days were you tired a lot during the past week? _____
    How tired have you been usually, on a scale from 1 to 10? _____

11. Have you been sensitive to bright light during the last week? ☐ 1. Yes ☐ 2. No (If No go to 12)
    How many days were you light sensitive during the last week? _____
    How bad is the sensitivity usually, on a scale from 1 to 10? _____

12. Have you been sensitive to loud noise during the last week? ☐ 1. Yes ☐ 2. No
    How many days were you sensitive to loud noise during the last week? _____
    How bad is the noise sensitivity usually, on a scale from 1 to 10? _____

APPENDIX C-6

A Multidisciplinary Evaluation of Mild TBI: Early Predictors of Outcome - Well Being Rating Scale

Study ID#: __ __ __
Interview Date: __ __/ __ __/ __ __
Interviewer's ID#: __ __ __

Instructions: This section of the examination contains questions about how you feel and how things have been going with you. For each question check the answer which best applies to you.

1. How have you been feeling in general during the past month? (P)
   a. In excellent spirits [5] ☐
   b. In very good spirits [4] ☐
   c. In good spirits mostly [3] ☐
   d. I have been up and down in spirits a lot [2] ☐
   e. In low spirits mostly [1] ☐
   f. Refused [88] ☐
   g. Don't know [99] ☐

2. How often were you bothered by any illness, bodily disorder, aches or pains during the past month? (G)
   a. Every day [0] ☐
   b. Almost every day [1] ☐
   c. About half of the time [2] ☐
   d. Now and then but less than half the time [3] ☐
   e. Rarely [4] ☐
   f. None of the time [5] ☐
   g. Refused [88] ☐
   h. Don't know [99] ☐

3. Did you feel depressed during the past month? (D)
   a. Yes – to the point that I felt like taking my life [0] ☐
   b. Yes – to the point that I didn't care about anything [1] ☐
   c. Yes – very depressed almost every day [2] ☐
   d. Yes – quite depressed several times [3] ☐
   e. Yes – a little depressed now and then [4] ☐
   f. No – never felt depressed at all [5] ☐
   g. Refused [88] ☐
   h. Don't know [99] ☐

4. Have you been in firm control of your behavior, thoughts, emotions or feelings during the past month? (S)
   a. Yes, definitely so [5] ☐
   b. Yes, for the most part [4] ☐
   c. Generally so [3] ☐
   d. Not too well [2] ☐
   e. No and I am somewhat disturbed [1] ☐
   f. No and I am very disturbed [0] ☐
   g. Refused [88] ☐
   h. Don't know [99] ☐

5. Have you been bothered by nervousness during the past month? (A)
   a. Extremely so, to the point where I could not work or take care of things. [0] ☐
   b. Very much so [1] ☐
   c. Quite a bit [2] ☐
   d. Some, enough to bother me [3] ☐
   e. A little [4] ☐
   f. Not at all [5] ☐
   g. Refused [88] ☐
   h. Don't know [99] ☐

6. How much energy, pep or vitality did you have during the past month? (V)

a.	Very full of energy, lots of pep	[5]	☐
b.	Fairly energetic most of the time	[4]	☐
c.	My energy varies quite a bit	[3]	☐
d.	Generally low energy or pep	[2]	☐
e.	Very low in energy or pep most of the time	[1]	☐
f.	No energy or pep at all, I felt drained, sapped	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

7. I felt downhearted and blue during the past month: (D)

a.	None of the time	[5]	☐
b.	A little of the time	[4]	☐
c.	Some of the time	[3]	☐
d.	A good bit of the time	[2]	☐
e.	Most of the time	[1]	☐
f.	All of the time	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

8. Were you generally tense or did you feel any tension during the past month? (A)

a.	Yes, extremely tense most or all of the time	[0]	☐
b.	Yes, very tense most of the time	[1]	☐
c.	Not generally tense but did feel fairly tense several times	[2]	☐
d.	I felt a little tense a few times	[3]	☐
e.	My general tension level was quite low	[4]	☐
f.	I never felt tense or any tension at all	[5]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

9. How happy, satisfied or pleased have you been with your personal life during the past month? (P)

a.	Extremely happy, could not have been more satisfied or pleased	[5]	☐
b.	Very happy most of the time	[4]	☐
c.	Generally satisfied, pleased	[3]	☐
d.	Sometimes fairly happy	[2]	☐
e.	Generally dissatisfied, unhappy	[1]	☐
f.	Very dissatisfied or unhappy most or all of the time	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

10. Did you feel healthy enough to carry out the things you like to do or had to do during the past month? (G)

a.	Yes, definitely so	[5]	☐
b.	For the most part	[4]	☐
c.	Health problems limited me in some important ways	[3]	☐
d.	I was only healthy enough to take care of myself	[2]	☐
e.	I needed some help in taking care of myself	[1]	☐
f.	I needed someone to help me with most or all of the things I had to do	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

11. Have you felt so sad, discouraged or hopeless or had so many problems that you wondered if anything was worthwhile during the past month? (D)
    a. Extremely so, to the point that I have just about given up [0] ☐
    b. Very much so [1] ☐
    c. Quite a bit [2] ☐
    d. Some, enough to bother me [3] ☐
    e. A little bit [4] ☐
    f. Not at all [5] ☐
    g. Refused [88] ☐
    h. Don't know [99] ☐

12. I woke up feeling fresh and rested during the past month: (V)
    a. None of the time [0] ☐
    b. A little of the time [1] ☐
    c. Some of the time [2] ☐
    d. A good bit of the time [3] ☐
    e. Most of the time [4] ☐
    f. All of the time [5] ☐
    g. Refused [88] ☐
    h. Don't know [99] ☐

13. Have you been concerned, worried or had any fears about your health during the past month? (G)
    a. Extremely so [0] ☐
    b. Very much so [1] ☐
    c. Quite a bit [2] ☐
    d. Some but not a lot [3] ☐
    e. Practically never [4] ☐
    f. Not at all [5] ☐
    g. Refused [88] ☐
    h. Don't know [99] ☐

14. Have you had any reason to wonder if you were losing your mind or losing control over the way you act, talk, think, feel or of your memory during the past month? (S)
    a. Not at all [5] ☐
    b. Only a little [4] ☐
    c. Some but not enough to be concerned or worried about [3] ☐
    d. Some and I'm a little concerned [2] ☐
    e. Some and I'm quite concerned [1] ☐
    f. Very much so and I am very concerned [0] ☐
    g. Refused [88] ☐
    h. Don't know [99] ☐

15. My daily life was full of things that were interesting to me during the past month. (P)
    a. None of the time [0] ☐
    b. A little of the time [1] ☐
    c. Some of the time [2] ☐
    d. A good bit of the time [3] ☐
    e. Most of the time [4] ☐
    f. All of the time [5] ☐
    g. Refused [88] ☐
    h. Don't know [99] ☐

16. Did you feel active, vigorous or dull, sluggish during the past month? (V)

a.	Very active, vigorous every day	[5]	☐
b.	Mostly active, vigorous – never really dull, sluggish	[4]	☐
c.	Fairly active, vigorous – seldom dull, sluggish	[3]	☐
d.	Fairly dull, sluggish – seldom active, vigorous	[2]	☐
e.	Mostly dull, sluggish – never really active, vigorous	[1]	☐
f.	Very dull, sluggish every day	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

17. Have you been anxious, worried or upset during the past month? (A)

a.	Extremely so – to the point of being sick or almost sick	[0]	☐
b.	Very much so	[1]	☐
c.	Quite a bit	[2]	☐
d.	Some, enough to bother me	[3]	☐
e.	A little bit	[4]	☐
f.	Not at all	[5]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

18. I was emotionally stable and sure of myself during the past month: (S)

a.	None of the time	[0]	☐
b.	A little of the time	[1]	☐
c.	Some of the time	[2]	☐
d.	A good bit of the time	[3]	☐
e.	Most of the time	[4]	☐
f.	All of the time	[5]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

19. Did you feel relaxed, at ease or high strung, tight or keyed-up during the past month? (A)

a.	Relaxed and at ease all month	[5]	☐
b.	Relaxed and at ease most of the time	[4]	☐
c.	Generally felt relaxed but at times felt fairly high strung	[3]	☐
d.	Generally felt high strung but at times felt fairly relaxed	[2]	☐
e.	High strung, tight or keyed-up most of the time	[1]	☐
f.	Felt high strung, tight or keyed-up the whole month	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

20. I felt cheerful, lighthearted during the past month: (P)

a.	None of the time	[0]	☐
b.	A little of the time	[1]	☐
c.	Some of the time	[2]	☐
d.	A good bit of the time	[3]	☐
e.	Most of the time	[4]	☐
f.	All of the time	[5]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

21. I felt tired, worn out, used up or exhausted during the past month: (V)

a.	None of the time	[5]	☐
b.	A little of the time	[4]	☐
c.	Some of the time	[3]	☐
d.	A good bit of the time	[2]	☐
e.	Most of the time	[1]	☐
f.	All of the time	[0]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

22. Have you been under or felt you were under any strain, stress or pressure during the past month? (A)

a.	Yes, almost more than I could bear or stand	[0]	☐
b.	Yes, quite a bit of pressure	[1]	☐
c.	Yes some, more than usual	[2]	☐
d.	Yes some, but about usual	[3]	☐
e.	Yes, a little	[4]	☐
f.	Not at all	[5]	☐
g.	Refused	[88]	☐
h.	Don't know	[99]	☐

APPENDIX C-7
A Multidisciplinary Evaluation of Mild TBI – BESS Assessment

Study ID #: __ __ __
Testing Date: __ __/ __ __/ __ __
Evaluator's ID #: __ __ __

This form is to be returned to the Coordination Office at the National Study Center within 24 hours of completion.

Subject can stand erect and unsupported for 2-3 minutes with eyes open ☐ Yes ☐ No
If **No** balance component not tested during this session

Dominant Leg: ☐ Right ☐ Left

BESS Types of Errors

1. Hands lifted off iliac crest
2. Opening eyes
3. Step, stumble or fall
4. Moving hip into >30 degrees abduction or flexion, or excessive trunk flexion/side-bending
5. Lifting forefoot or heel off surface
6. Remaining out of test position > 5 sec

The maximum total number of errors for any single condition is 10. If a subject commits multiple errors simultaneously, only one error is recorded.
Spotter must be present throughout BESS testing, spotter is to guard subject and assist with return to testing position if needed

BESS Score (# of errors)	**Foot Tested**	**FIRM surface**	**FOAM Surface**
Double Leg Stance			
Single Leg Stance (non-dominant foot)			
Tandem Stance (non-dominant foot behind)			
Total Scores:			
Total BESS Score:			

Comments:

Appendix D - Supporting Data

D-1 **Table 9-12**

D-2 **Figures 1-5**

D-3 **Figures 11-21**

D-4 **Tables 13-16**

APPENDIX D1 – Tables 9-12

Table 9: Comparison of Mean Balance Data for Physical Symptoms at 3, 6 and 12 Months

	3 months					6 months					12 months				
	Physical Symptoms		No Physical Symptoms			Physical Symptoms		No Physical Symptoms			Physical Symptoms		No Physical Symptoms		
	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p
Balance Composite	80.1	8.0	81.9	13.8	0.55	79.1	8.4	82.4	6.0	0.26	79.7	8.4	78.8	6.5	0.76
BESS Firm Errors	10.8	5.3	7.6	5.9	0.18	10.9	5.7	6.1	3.9	0.02	10.5	6.1	9.5	6.9	0.74
BESS Foam Errors	19.3	8.8	19.7	9.6	0.93	20.1	8.6	14.9	6.6	0.11	19.1	8.8	19.1	12.3	0.99
BESS Total Errors	30.1	13.5	27.2	14.3	0.62	31	13.7	21	8.7	0.04	29.6	13.9	28.6	18.4	0.90

Table 10: Comparison of Mean Balance Data for Cognitive Symptoms at 3, 6 and 12 Months

	3 months					6 months					12 months				
	Cognitive Symptoms		No Cognitive Symptoms			Cognitive Symptoms		No Cognitive Symptoms			Cognitive Symptoms		No Cognitive Symptoms		
	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p
Balance Composite	80.4	8.3	80.8	7.2	0.89	78.5	8.7	81.1	7.2	0.41	80.6	7.6	78.5	7.9	0.52
BESS Firm Errors	11.1	5.8	8.2	5.1	0.16	10.3	5.1	8.8	6.0	0.51	10	5.3	10.3	7.2	0.92
BESS Foam Errors	19.9	9.5	18.9	8.5	0.78	18.5	7.2	18.5	9.3	0.98	17.6	9.0	20.3	10.8	0.52
BESS Total Errors	31	14.7	27.1	12.3	0.45	28.8	11.1	27.3	14.7	0.76	27.6	13.7	30.6	16.9	0.65

Table 11: Comparison of Mean Balance Data for Emotional Symptoms at 3, 6 and 12 Months

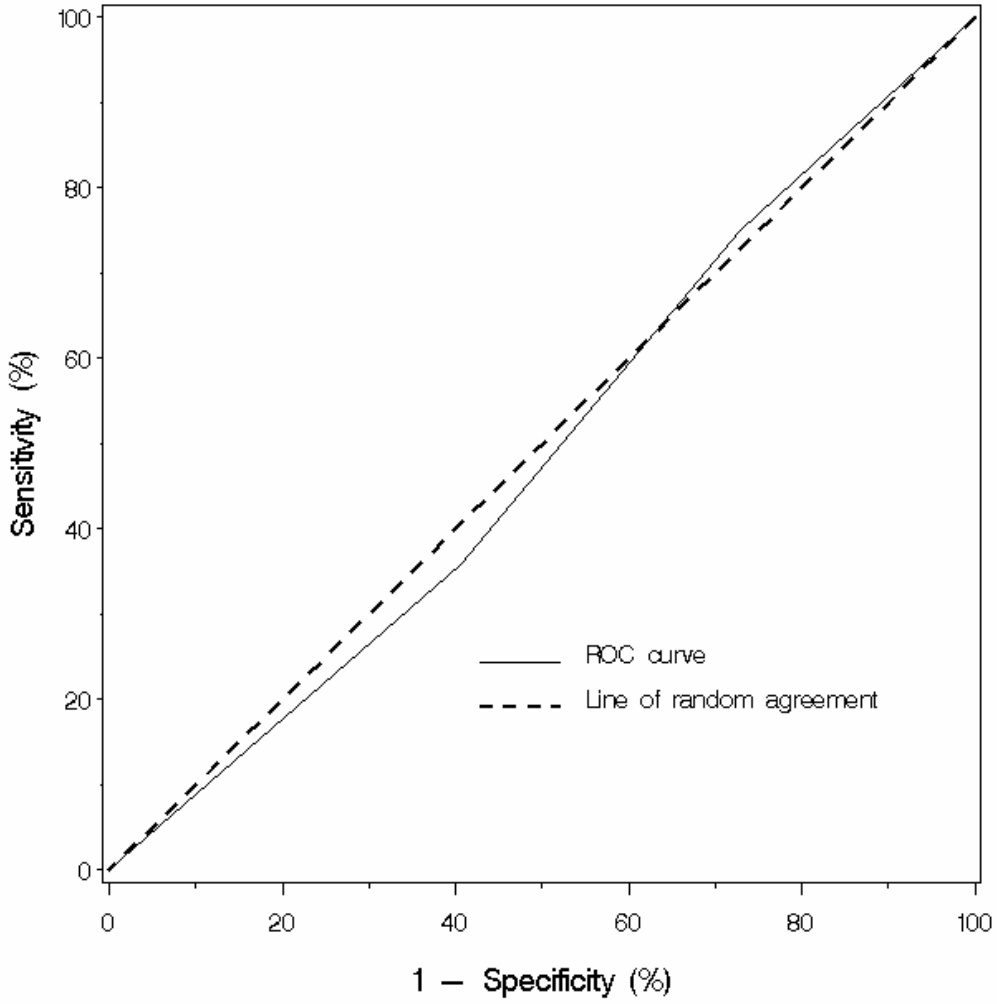
	3 months					6 months					12 months				
	Emotional Symptoms		No Emotional Symptoms			Emotional Symptoms		No Emotional Symptoms			Emotional Symptoms		No Emotional Symptoms		
	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p
Balance Composite	79.2	8.6	81.6	7.1	0.42	78.1	9.5	81.4	6.4	0.33	79.4	7.3	79.4	8.1	0.99
BESS Firm Errors	12.5	4.3	7.7	5.7	0.02	10.5	5.1	8.6	6.0	0.38	12	6.8	9.1	5.9	0.33
BESS Foam Errors	20.3	8.1	18.8	9.6	0.64	19.3	6.8	17.9	9.5	0.68	21.3	10.5	17.9	9.7	0.47
BESS Total Errors	32.8	11.8	26.4	14.5	0.21	29.8	10.7	26.5	14.8	0.52	33.3	16.6	26.9	14.6	0.39

Table 12: Comparison of Mean Balance Data for 4 or more Symptoms at 3, 6 and 12 Months

	3 months					6 months					12 months				
	4+ Symptoms		< 4 Symptoms			4+ Symptoms		< 4 Symptoms			4+ Symptoms		< 4 Symptoms		
	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p	Mean	STD	Mean	STD	p
Balance Composite	76.9	8.1	82.3	7.0	0.11	76.6	10.3	81.3	6.6	0.30	81.6	6.8	78.8	7.9	0.46
BESS Firm Errors	14.0	3.7	7.7	5.2	0.002	11.4	5.3	8.7	5.7	0.28	12.2	6.5	9.5	6.2	0.44
BESS Foam Errors	22.8	7.9	17.8	9.1	0.16	22.1	5.8	17.2	8.8	0.11	23.2	9.1	17.9	10.0	0.30
BESS Total Errors	36.8	11.0	25.6	13.4	0.03	33.6	9.7	25.8	13.7	0.13	35.4	14.7	27.4	15.4	0.33

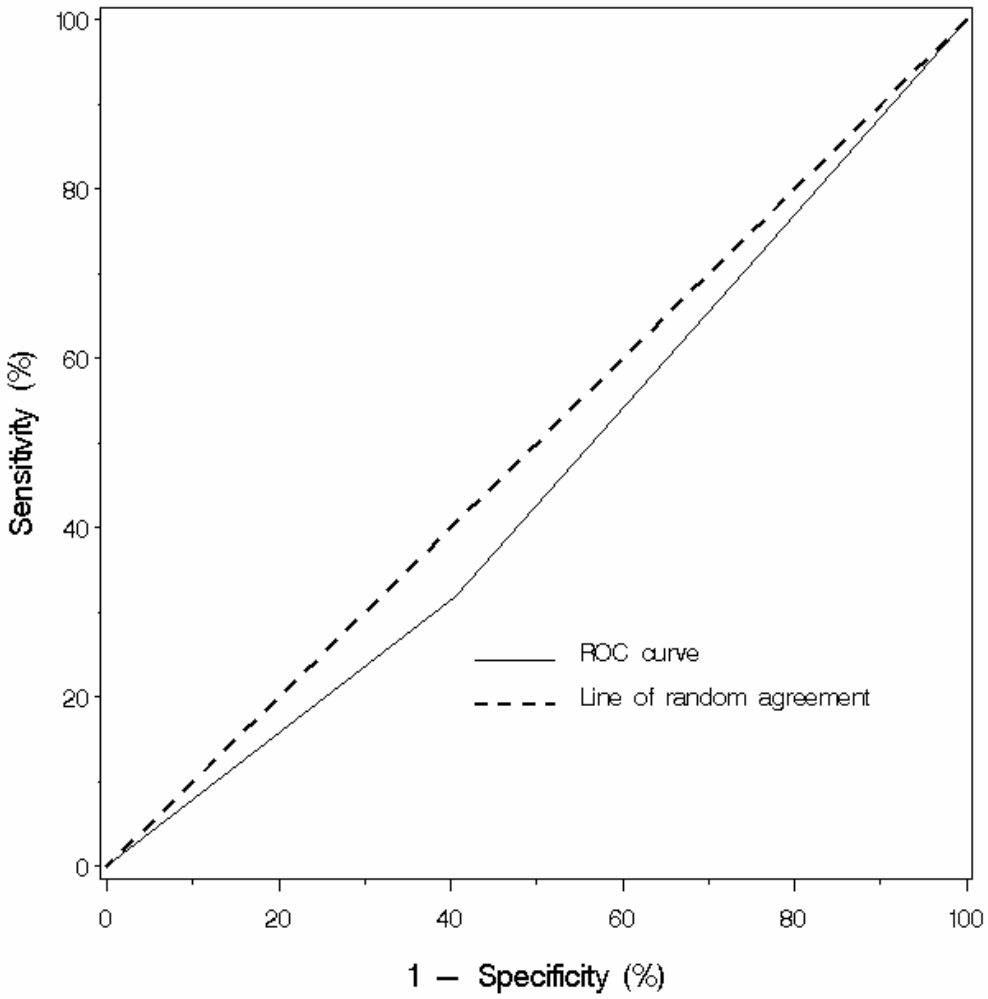
APPENDIX D-2: Figures 1-6

Figure 1: ROC Curve for S100B
Relationship With 4+ Symptoms at 3 Months



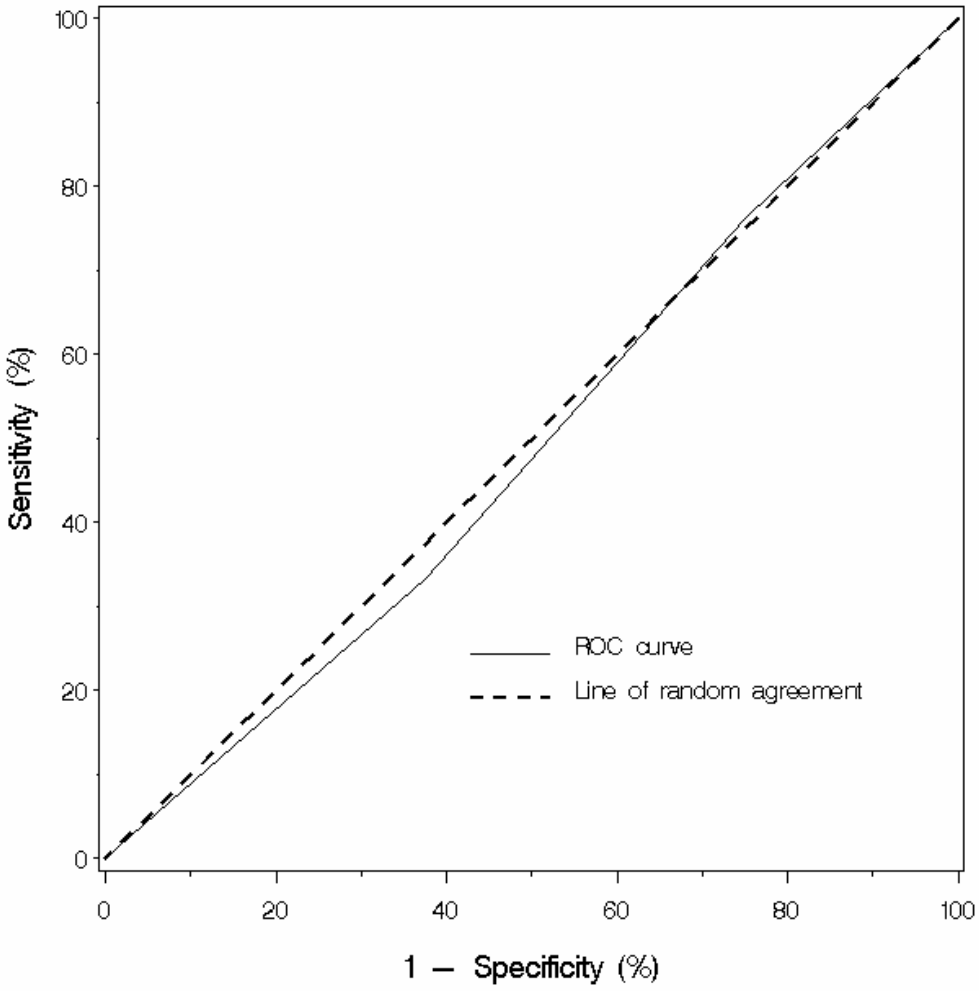
Area under the curve = 49%

Figure 2: ROC Curve for S100B
Relationship With 4+ Symptoms at 6 Months



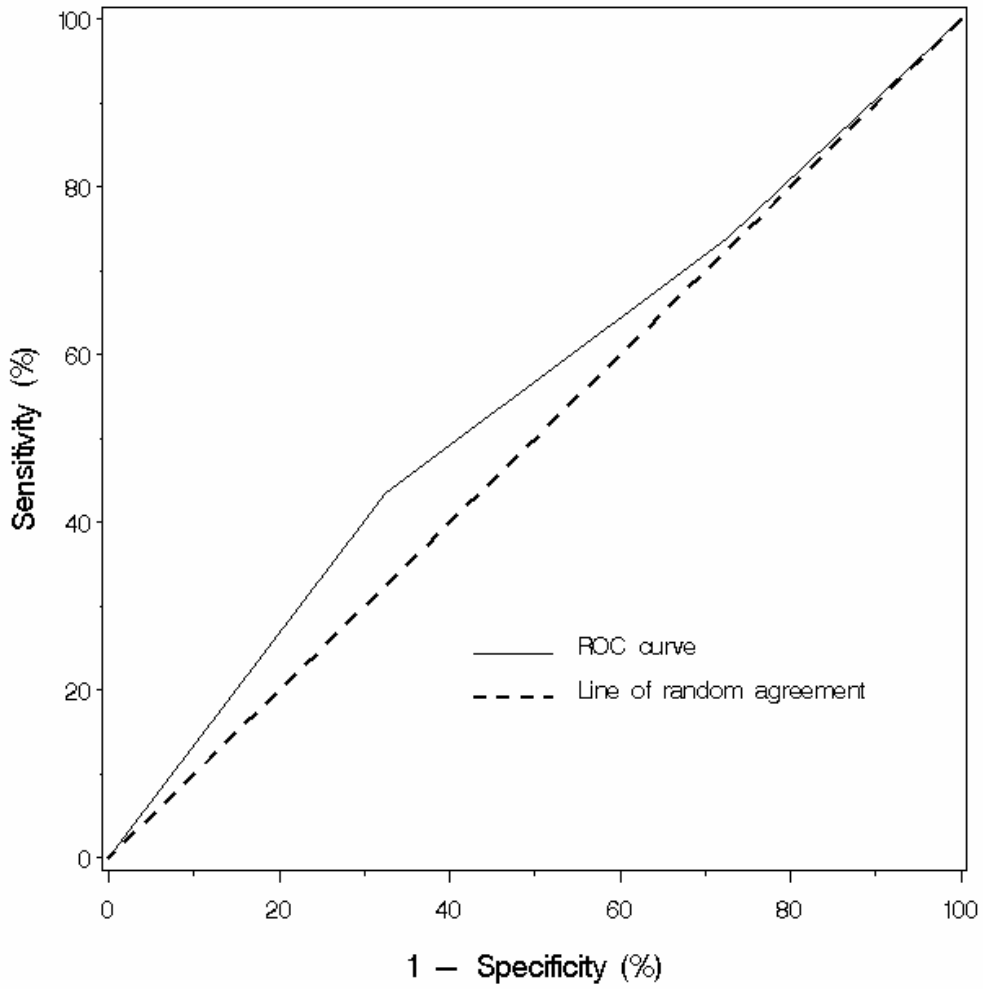
Area under the curve = 46%

Figure 3: ROC Curve for S100B
Relationship With 4+ Symptoms at 12 Months



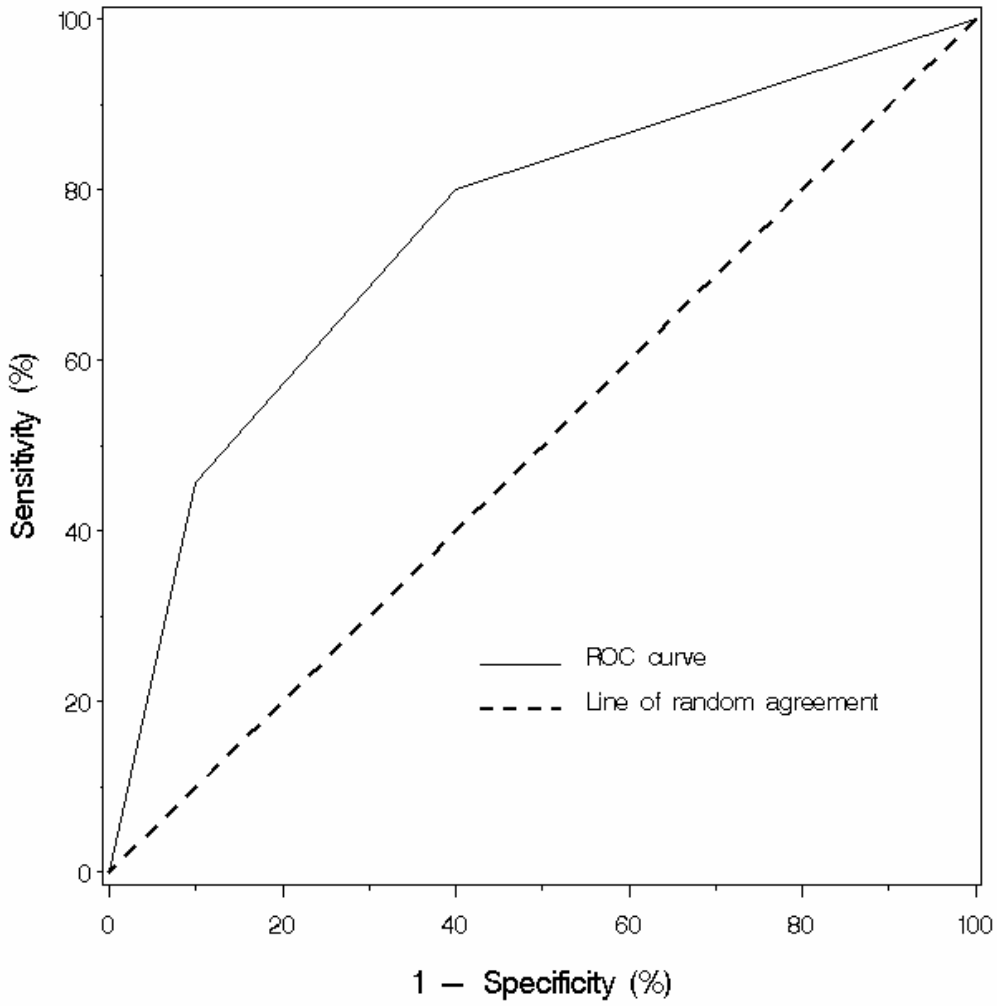
Area under the curve = 49%

Figure 4: ROC Curve for S100B
Relationship With Inability to Work at 3 Months



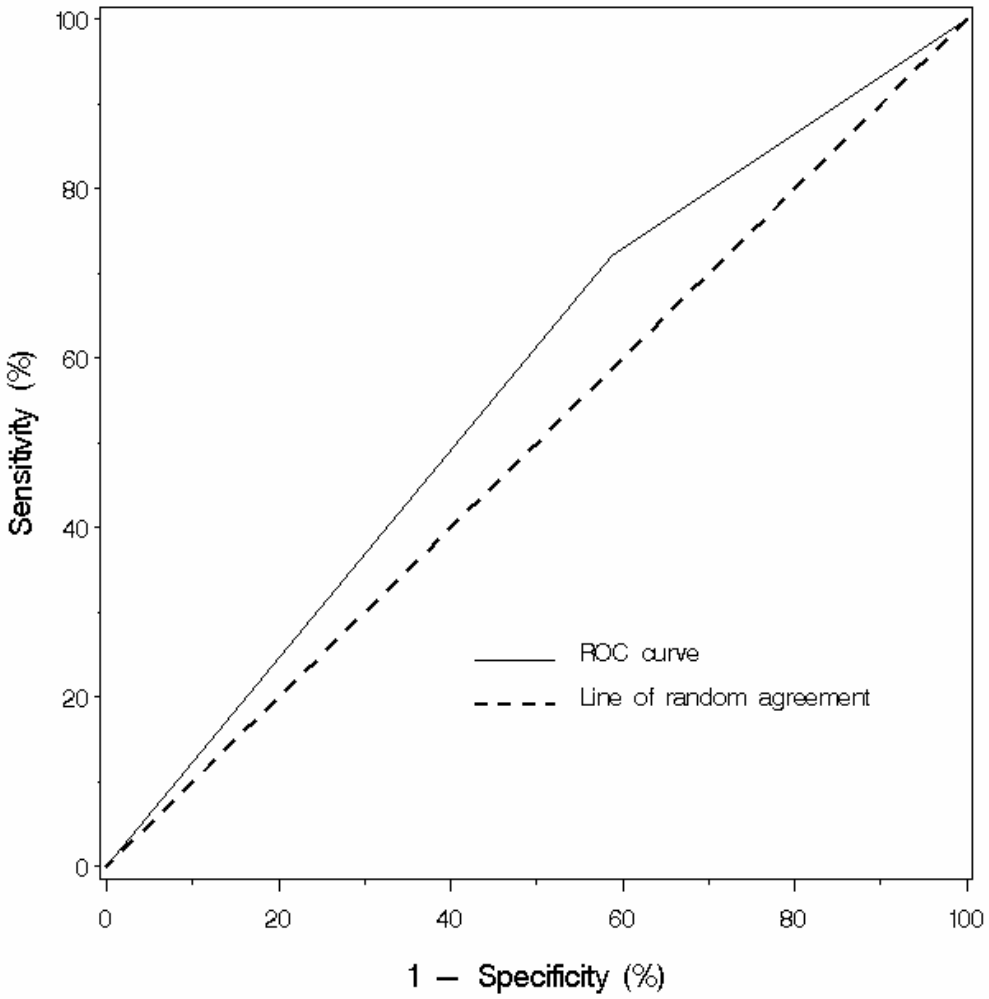
Area under the curve = 54%

Figure 5: ROC Curve for S100B
Relationship With Extracranial Injuries



Area under the curve = 75%

Figure 6: ROC Curve for S100B
Relationship With Emotional Symptoms at 3—10 Days



Area under the curve = 57%

APPENDIX D-3: Figure 11-21

Figure 11: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Dizziness At 3-10 Days Post-Injury

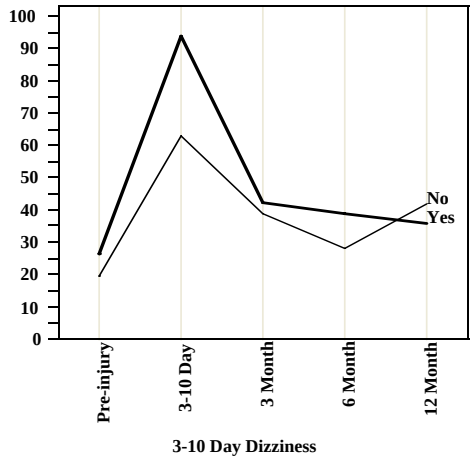


Figure 12: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Blurry/Double Vision At 3-10 Days Post-Injury

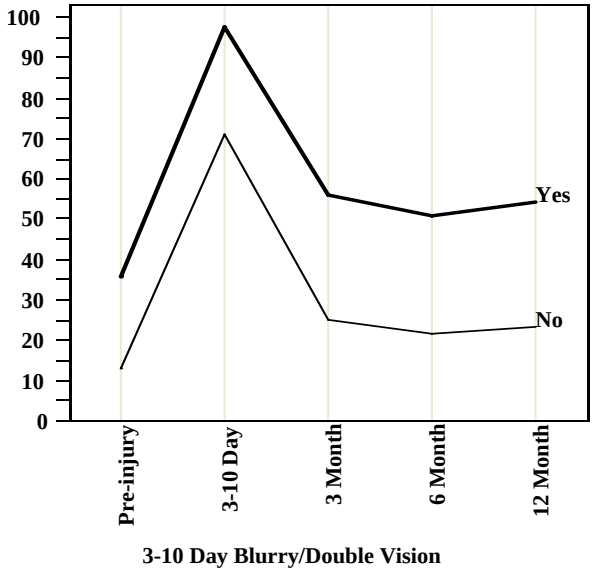


Figure 13: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Fatigue At 3-10 Days Post-Injury

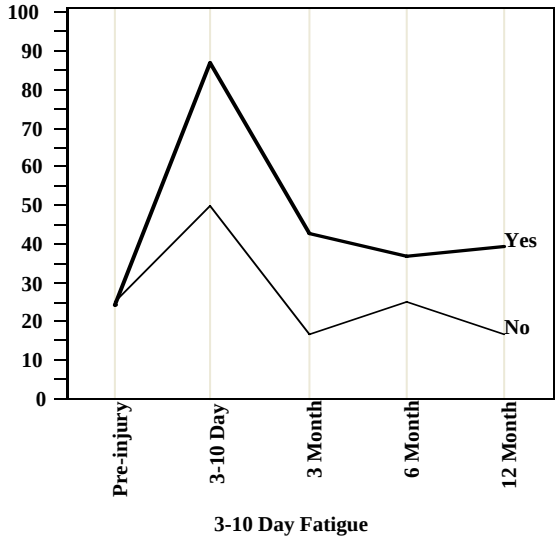


Figure 14: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Sensitivity to Light At 3-10 Days Post-Injury

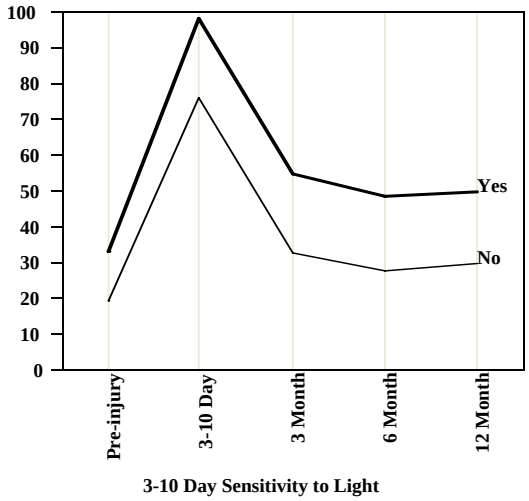


Figure 15: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Sensitivity to Noise At 3-10 Days Post-Injury

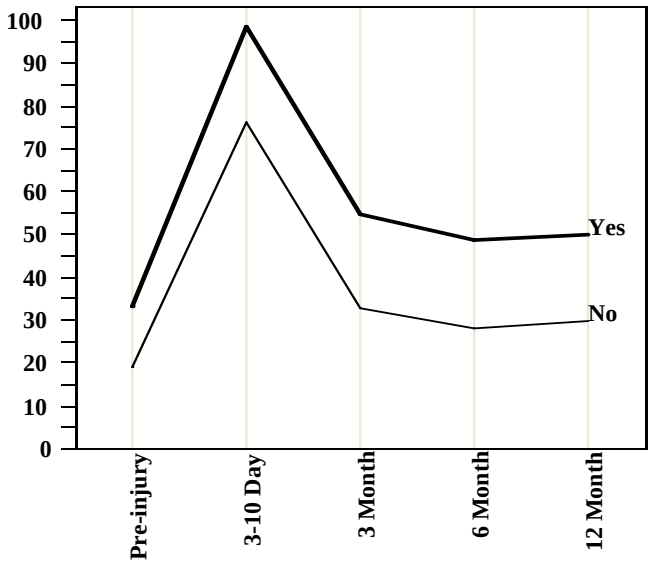


Figure 16: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Difficulty Concentrating At 3-10 Days Post-Injury

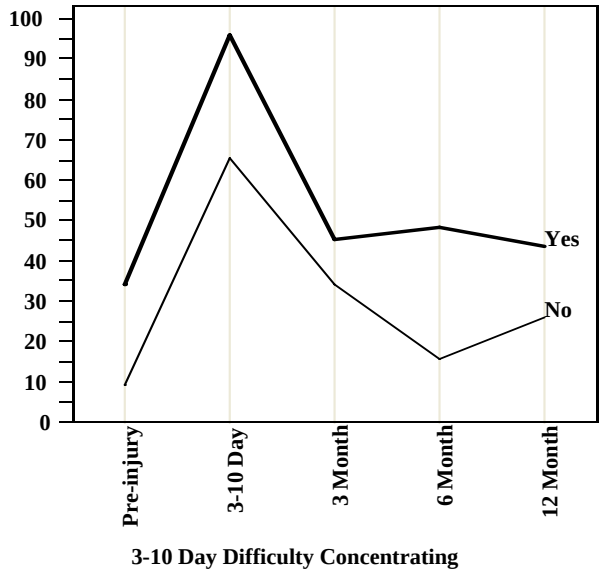


Figure 17: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Memory Problems At 3-10 Days Post-Injury

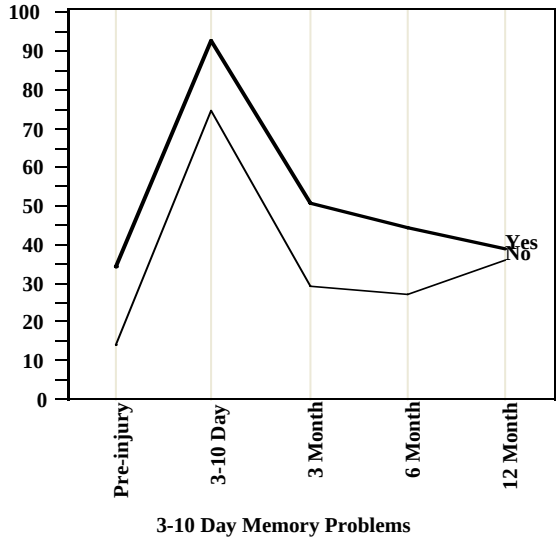


Figure 18: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Trouble Thinking At 3-10 Days Post-Injury

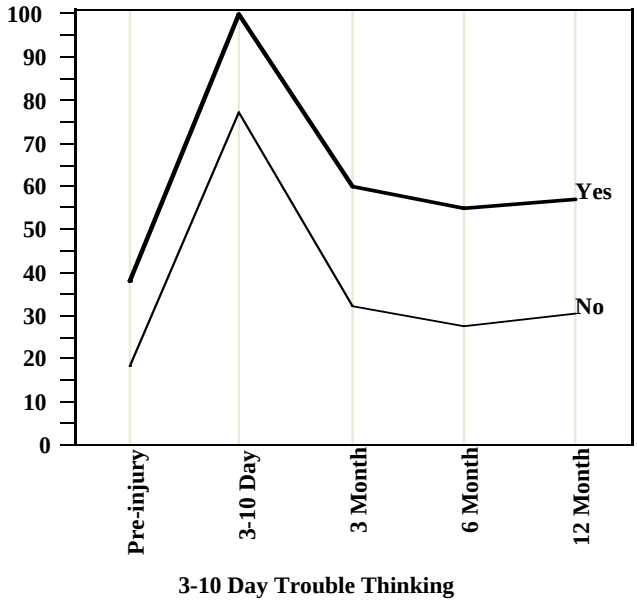


Figure 19: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Anxiety At 3-10 Days Post-Injury

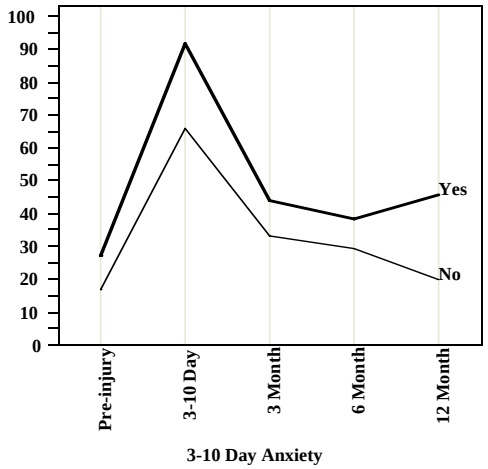


Figure 20: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Depression At 3-10 Days Post-Injury

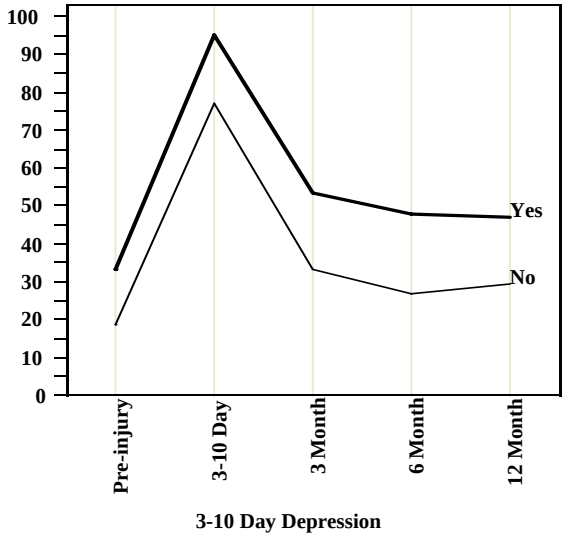
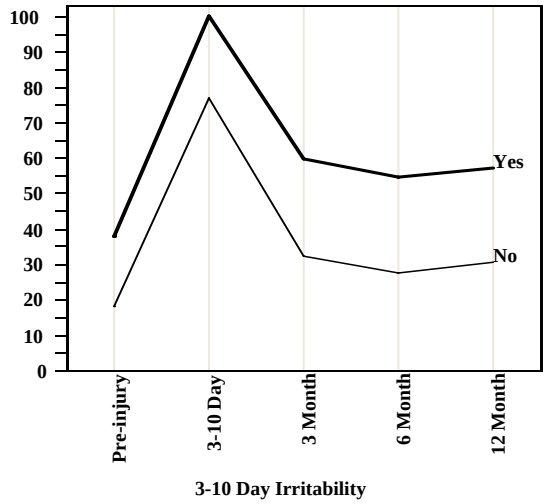


Figure 21: Reporting Of 4 Or More Symptoms Among Subjects With Or Without Irritability At 3-10 Days Post-Injury



APPENDIX D-4: Tables 14-16

Table 14: The Univariate Effect of Independent Variables on Various 3 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
	Est	p-value	OR	p-value	Est	p-value	Est	p-value	OR	p-value
S100B	-1.90	0.52	1.82	0.76	-0.80	0.64	12.30	0.55	50.00	0.08
Mid tertile vs. low tertile			1.23	0.70					2.04	0.22
High tertile vs. low tertile			0.97	0.95					1.25	0.70
SRT thru put – Initial	-0.01	0.14	1.00	0.17	0.00	0.51	-0.04	0.32	1.00	0.97
Mid tertile vs. low tertile			1.20	0.71					1.37	0.57
High tertile vs. low tertile			0.55	0.24					1.32	0.62
SRT thruput – 7-10 day (ANAM)	-0.01	0.56	1.00	0.47	0.00	0.95	-0.08	0.20	0.99	0.44
SCATBI										
Initial Encounter										
Recall	-0.07	0.04*	0.98	0.33	-0.03	0.11	-0.10	0.63	0.99	0.85
Mid tertile vs. low tertile			0.33	0.13					0.96	0.96
High tertile vs. low tertile			0.48	0.22					0.80	0.73
Reasoning	-0.03	0.39	0.99	0.78	-0.03	0.11	-0.02	0.94	1.03	0.27
Organization	0.01	0.75	1.02	0.39	0.01	0.69	0.20	0.37	1.00	0.99
Orientation	-0.06	0.23	1.00	1.00	-0.05	0.14	-0.50	0.11	0.96	0.23
Higher Function (Recall&Reasoning)	-0.02	0.29	0.99	0.65	-0.02	0.16	-0.02	0.85	1.01	0.68
7-10 Day Visit										
Recall	-0.05	0.17	0.99	0.63	-0.02	0.23	-0.20	0.31	1.03	0.34
Mid tertile vs. low tertile			0.11	0.08					1.41	0.77
High tertile vs. low tertile			0.46	0.29					1.92	0.46
Reasoning	-0.04	0.20	0.98	0.35	-0.02	0.33	-0.20	0.40	1.01	0.71
Organization	-0.05	0.14	0.98	0.49	-0.03	0.14	-0.10	0.57	0.98	0.32
Orientation	-0.05	0.32	0.94	0.18	-0.02	0.54	-0.20	0.62	0.98	0.72
Higher Function	-0.03	0.15	0.99	0.45	-0.01	0.20	-0.10	0.36	1.01	0.43

Table 14: The Univariate Effect of Independent Variables on Various 3 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Balance										
Composite – Balance Master	-0.06	0.41	0.91	0.09	-0.02	0.67	-0.71	0.06	0.98	0.67
Error Points Firm – BESS	0.30	0.001**	1.27	0.02*	0.20	0.01*	1.20	0.04*	1.06	0.42
Error Points Foam – BESS	0.09	0.21	1.07	0.17	0.02	0.78	0.40	0.31	1.01	0.85
Total Error Points - BESS	0.09	0.03*	1.07	0.05	0.03	0.24	0.40	0.13	1.02	0.65
Covariates										
Age	0.04	0.08	1.02	0.21	0.01	0.72	0.10	0.57	1.01	0.45
Mid tertile vs. low tertile			2.04	0.17					2.78	0.07
High tertile vs. low tertile			1.83	0.20					1.69	0.32
Sex – Female	2.10	0.0002**	2.38	0.03*	1.47	<0.001**	14.03	0.002**	0.62	0.28
Previous Brain Injury	-1.90	0.05	0.14	0.06	-1.06	0.09	-4.15	0.59	1.41	0.62
Motorized Vehicle	-0.34	0.58	0.92	0.47	-0.05	0.90	-2.08	0.67	0.95	0.67
Baseline Depression	2.24	0.002**	3.56	0.01*	1.18	0.01*	16.20	0.002**	4.17	0.008**
Injury other than to head	0.52	0.38	1.37	0.42	0.20	0.59	6.07	0.18	1.59	0.29
Lifetime Alcohol Dependence	-0.90	0.25	0.70	0.50	-0.37	0.44	-8.86	0.15	1.37	0.56
<= High School	1.20	0.05	2.08	0.07	0.73	0.05	2.70	0.57	1.49	0.37
Symptoms –Pre Injury										
Headache	1.30	0.03*	1.99	0.09	0.77	0.04*	3.70	0.43	1.09	0.84
Anxiety	2.20	0.003	3.56	0.01*	1.00	0.03*	23.80	<0.0001**	1.82	0.26
Depression	2.00	0.02*	7.18	0.004	1.30	0.01*	17.40	0.005**	3.23	0.05
Concentration	0.53	0.49	1.70	0.30	0.30	0.53	9.70	0.11	1.82	0.26
Dizziness	-0.07	0.95	0.44	0.33	0.54	0.44	-0.68	0.93	3.85	0.08
Memory	0.12	0.86	0.83	0.69	0.27	0.53	5.42	0.30	3.70	0.006**
Vision	0.31	0.79	3.78	0.12	0.76	0.30	-3.60	0.69	0.80	0.80

Table 14: The Univariate Effect of Independent Variables on Various 3 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Thinking	0.99	0.44	1.42	0.68	0.34	0.66	7.80	0.39	4.55	0.09
Irritable	1.03	0.09	3.00	0.008**	0.71	0.06	7.70	0.10	2.04	0.10
Tired	0.70	0.24	1.41	0.39	0.73	0.05	1.36	0.77	1.54	0.34
Light Sensitivity	1.70	0.02*	3.21	0.02*	1.20	0.01*	-4.34	0.51	0.84	0.75
Noise Sensitivity	3.14	0.002**	5.56	0.04*	0.87	0.18	10.60	0.20	3.85	0.08
Physical	2.53	0.0003**	4.43	0.01*	1.84	<0.0001**	9.40	0.07	2.27	0.18
Emotional	1.70	0.003**	4.44	<0.001**	1.14	0.001**	12.40	0.005**	2.38	0.04*
Cognitive	0.57	0.35	1.44	0.36	0.49	0.19	9.18	0.05	3.33	0.006**
Symptoms –3-10 Days Post-Injury										
Headache	1.50	0.03*	1.56	0.34	1.04	0.01*	6.61	0.20	1.28	0.62
Anxiety	1.90	0.001	3.84	0.001**	0.90	0.01*	7.30	0.11	3.03	0.01*
Depression	1.30	0.02*	2.30	0.04*	0.95	0.01*	15.40	0.0005**	4.76	<0.001**
Concentration	1.60	0.01*	1.58	0.27	0.77	0.04*	6.30	0.21	2.70	0.04*
Dizziness	1.00	0.13	1.16	0.73	0.84	0.04*	1.70	0.76	4.35	0.01*
Memory	1.80	0.003**	2.51	0.02*	1.00	0.01*	12.60	0.006**	2.70	0.03*
Vision	1.40	0.02*	2.04	0.08	0.84	0.03*	4.00	0.39	1.47	0.38
Thinking	1.40	0.02*	3.12	0.007**	0.74	0.06	9.50	0.04*	3.23	0.008**
Irritable	1.70	0.01*	2.74	0.03*	1.00	0.01*	12.20	0.01*	3.57	0.02*
Tired	1.30	0.32	3.73	0.24	1.07	0.18	11.00	0.23	--	--
Light Sensitivity	1.40	0.02*	2.48	0.03*	1.01	0.06	3.20	0.49	1.35	0.47
Noise Sensitivity	1.90	0.003	3.14	0.008**	1.11	0.004**	9.30	0.05	2.38	0.05
Physical	1.60	0.61	--	--	0.15	0.94	8.90	0.65	--	--
Emotional	2.40	0.001**	8.41	0.006**	1.28	0.01*	18.80	0.0004**	4.55	0.05
Cognitive	2.00	0.01*	2.45	0.11	1.44	0.002**	9.60	0.11	3.13	0.08

Table 15: The Univariate Effect of Independent Variables on Various 6 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
	Est	p-value	OR	p-value	Est	p-value	Est	p-value	OR	p-value
S100B	-2.40	0.40	0.14	0.41	-0.48	0.79	14.84	0.46	2.56	0.77
Mid tertile vs. low tertile			1.69	0.35					0.53	0.51
High tertile vs. low tertile			1.25	0.68					0.67	0.64
SRT thru put – Initial	-0.00	0.47	1.00	0.68	-0.00	0.18	-0.04	0.31	0.99	0.13
Mid tertile vs. low tertile			1.40	0.53					0.75	0.71
High tertile vs. low tertile			1.34	0.59					0.39	0.30
SRT thruput – 7-10 day (ANAM)	-0.01	0.61	1.00	0.86	-0.00	0.75	-0.02	0.70	1.00	0.97
SCATBI										
Initial Encounter										
Recall	-0.01	0.81	1.01	0.80	-0.01	0.71	0.00	0.99	0.97	0.43
Mid tertile vs. low tertile			0.41	0.32					0.50	0.56
High tertile vs. low tertile			1.18	0.80					0.50	0.46
Reasoning	-0.00	0.98	0.98	0.34	-0.01	0.55	-0.02	0.94	1.03	0.44
Organization	0.04	0.18	1.05	0.10	0.01	0.61	0.28	0.25	1.03	0.46
Orientation	0.04	0.51	1.02	0.67	0.01	0.72	-0.29	0.43	0.93	0.10
Higher Function	0.00	0.99	0.99	0.66	-0.00	0.82	0.02	0.89	1.00	0.87
7-10 Day Visit										
Recall	0.01	0.70	1.01	0.60	-0.02	0.48	-0.10	0.66	1.00	0.92
Mid tertile vs. low tertile			0.20	0.22					2.50	0.51
High tertile vs. low tertile			0.93	0.93					0.65	0.73
Reasoning	0.01	0.81	1.01	0.73	-0.01	0.52	0.01	0.97	1.04	0.35
Organization	-0.04	0.31	0.99	0.81	-0.03	0.17	-0.17	0.44	0.95	0.15
Orientation	-0.14	0.01*	0.95	0.19	-0.06	0.05*	-0.50	0.17	--	--
Higher Function	0.01	0.69	1.01	0.63	-0.01	0.55	-0.01	0.92	1.02	0.53

Table 15: The Univariate Effect of Independent Variables on Various 6 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Balance										
Composite – Balance Master	-0.10	0.27	0.92	0.18	-0.07	0.20	-0.56	0.18	0.92	0.31
Error Points Firm – BESS	0.20	0.10	1.09	0.27	0.12	0.08	0.71	0.22	1.11	0.33
Error Points Foam – BESS	0.11	0.19	1.08	0.18	0.04	0.40	0.19	0.62	0.96	0.66
Total Error Points - BESS	0.08	0.12	1.05	0.19	0.04	0.20	0.21	0.41	1.01	0.88
Covariates										
Age	0.01	0.61	1.00	0.78	0.00	0.87	0.01	0.98	1.04	0.12
Mid tertile vs. low tertile			1.00	1.00					6.67	0.10
High tertile vs. low tertile			1.33	0.55					6.25	0.10
Sex – Female	1.15	0.04*	2.27	0.05*	0.76	0.03*	10.45	0.02*	1.23	0.74
Previous Brain Injury	-0.88	0.31	0.55	0.39	-0.62	0.25	-12.07	0.10	--	--
Motorized Vehicle	-0.49	0.40	0.97	0.77	-0.12	0.75	-2.07	0.66	1.01	0.94
Baseline Depression	0.53	0.44	2.04	0.16	0.40	0.36	11.90	0.02*	2.00	0.35
Injury other than to head	0.02	0.97	1.04	0.92	0.41	0.24	6.24	0.17	0.77	0.68
Lifetime Alcohol Dependence	0.53	0.44	1.58	0.37	0.63	0.15	1.25	0.83	0.45	0.46
<= High School	0.29	0.62	0.96	0.93	0.29	0.42	-3.74	0.43	2.08	0.27
Symptoms –Pre Injury										
Headache	1.70	0.002**	4.49	<0.001**	0.84	0.02*	9.68	0.04*	1.45	0.57
Anxiety	2.05	0.01*	3.64	0.02*	1.16	0.01*	19.35	<0.001**	3.03	0.15
Depression	2.24	0.01*	11.67	0.002**	1.21	0.02*	15.81	0.01*	2.04	0.41
Concentration	1.77	0.01*	3.42	0.02*	1.10	0.01*	14.62	0.01*	1.67	0.48
Dizziness	1.85	0.09	2.50	0.25	1.33	0.05*	7.99	0.36	4.35	0.12
Memory	0.92	0.14	1.75	0.23	0.74	0.06	6.48	0.21	1.79	0.40
Vision	1.19	0.24	1.85	0.41	1.06	0.10	11.15	0.16	1.27	0.83

Table 15: The Univariate Effect of Independent Variables on Various 6 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Thinking	0.95	0.42	1.82	0.48	0.51	0.50	8.64	0.32	1.54	0.71
Irritable	1.24	0.03*	2.68	0.02*	0.78	0.03*	5.25	0.25	1.69	0.42
Tired	0.99	0.07	2.16	0.08	0.34	0.33	4.10	0.37	3.33	0.14
Light Sensitivity	1.29	0.07	1.14	0.80	0.82	0.07	0.45	0.94	0.99	0.99
Noise Sensitivity	2.13	0.02*	4.82	0.03*	0.64	0.27	19.25	0.005**	1.08	0.95
Physical	1.39	0.04	4.68	0.02*	0.65	0.12	8.77	0.08	2.63	0.38
Emotional	1.46	0.01*	2.85	0.01*	1.01	0.004**	10.75	0.02*	2.17	0.23
Cognitive	1.59	0.004**	2.85	0.01*	1.04	0.003**	11.34	0.01*	1.37	0.63
Symptoms –3-10 Days Post-Injury										
Headache	0.40	0.52	1.48	0.42	0.25	0.53	0.81	0.87	1.41	0.69
Anxiety	1.61	0.003**	3.79	0.003**	1.01	0.003**	12.16	0.01*	4.76	0.06
Depression	0.91	0.10	2.50	0.03*	0.72	0.04*	10.44	0.02*	2.08	0.29
Concentration	1.80	0.001**	5.00	0.002**	0.81	0.02*	7.39	0.13	2.63	0.24
Dizziness	1.04	0.10	1.62	0.34	0.55	0.17	4.90	0.36	1.32	0.74
Memory	1.50	0.005**	2.14	0.08	0.92	0.01*	15.12	0.001**	--	--
Vision	1.54	0.004**	2.37	0.05*	0.75	0.04*	6.07	0.19	2.86	0.13
Thinking	1.88	0.001**	3.20	0.01*	0.98	0.01*	12.94	0.01*	3.85	0.05*
Irritable	1.94	0.001**	3.02	0.02*	1.19	0.01*	11.56	0.02*	4.76	0.15
Tired	-0.03	0.97	1.76	0.50	-0.19	0.77	-0.96	0.90	--	--
Light Sensitivity	1.45	0.01*	2.46	0.04*	0.90	0.01*	8.41	0.07	1.61	0.48
Noise Sensitivity	1.50	0.01*	2.33	0.06	0.99	0.01*	14.02	0.004**	1.49	0.56
Physical	0.73	0.71	--	--	1.25	0.32	11.33	0.40	--	--
Emotional	2.45	<0.001**	7.18	0.01*	1.69	<0.001**	17.72	0.001**	--	--
Cognitive	2.09	0.001**	8.30	0.006**	1.04	0.01*	11.03	0.06	--	--

Table 16: The Univariate Effect of Independent Variables on Various 12 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
	Est	p-value	OR	p-value	Est	p-value	Est	p-value	OR	p-value
S100B	-2.51	0.48	0.16	0.49	-2.90	0.16	-17.37	0.41	100.00	0.10
Mid tertile vs. low tertile			1.65	0.49					1.09	0.95
High tertile vs. low tertile			1.94	0.34					2.08	0.53
SRT thruput – Initial	-0.01	0.27	1.00	0.49	-0.00	0.41	-0.02	0.73	1.00	0.59
Mid tertile vs. low tertile			1.13	0.83					0.64	0.67
High tertile vs. low tertile			0.74	0.62					1.04	0.96
SRT thruput – 7-10 day (ANAM)	-0.00	0.97	1.00	0.98	0.00	0.94	-0.08	0.21	0.97	0.03*
SCATBI										
Initial Encounter										
Recall	-0.09	0.01*	0.96	0.13	-0.05	0.02*	-0.29	0.15	0.96	0.38
Mid tertile vs. low tertile			1.14	0.87					1.00	1.00
High tertile vs. low tertile			0.34	0.14					0.37	0.43
Reasoning	-0.04	0.21	0.99	0.69	-0.03	0.12	-0.15	0.41	20.00	0.60
Organization	0.04	0.18	1.03	0.39	0.03	0.22	0.14	0.54	1.04	0.52
Orientation	-0.08	0.20	0.96	0.33	-0.05	0.25	-0.31	0.36	1.75	0.98
Higher Function	-0.03	0.06	0.98	0.28	-0.03	0.04*	-0.09	0.40	1.05	0.33
7-10 Day Visit										
Recall	-0.04	0.39	0.99	0.70	-0.03	0.28	0.09	0.69	0.98	0.74
Mid tertile vs. low tertile			0.75	0.82					--	--
High tertile vs. low tertile			0.71	0.73					--	--
Reasoning	-0.04	0.33	0.99	0.76	-0.03	0.34	-0.09	0.68	0.98	0.64
Organization	-0.05	0.14	0.99	0.67	-0.03	0.22	-0.23	0.22	0.92	0.03*
Orientation	-0.19	0.01*	0.96	0.37	-0.08	0.08	-0.76	0.02*	0.92	0.12
Higher Function	-0.02	0.33	1.00	0.77	-0.02	0.27	0.01	0.94	0.99	0.79

Table 16: The Univariate Effect of Independent Variables on Various 12 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Balance										
Composite – Balance Master	0.08	0.36	1.06	0.46	0.00	0.99	0.19	0.66	1.19	0.24
Error Points Firm – BESS	0.17	0.11	1.07	0.40	0.09	0.15	0.54	0.31	1.30	0.14
Error Points Foam – BESS	0.06	0.41	1.06	0.29	0.01	0.87	0.17	0.62	1.09	0.34
Total Error Points - BESS	0.05	0.24	1.04	0.30	0.02	0.49	0.16	0.46	1.08	0.21
Covariates										
Age	0.01	0.56	1.00	0.87	-0.01	0.59	0.29	0.06	1.05	0.09
Mid tertile vs. low tertile			4.52	0.02*					1.82	0.68
High tertile vs. low tertile			1.51	0.46					7.69	0.06
Sex – Female	2.37	<0.001**	3.03	0.02*	1.39	<0.001**	9.13	0.03*	0.84	0.82
Previous Brain Injury	-2.19	0.02*	0.29	0.13	-1.76	0.002**	-12.30	0.05*	--	--
Motorized Vehicle	-0.37	0.62	0.91	0.46	0.02	0.96	-2.60	0.57	1.02	0.91
Baseline Depression	0.55	0.57	1.26	0.72	0.89	0.12	10.85	0.05*	5.26	0.05*
Injury other than to head	0.10	0.88	0.99	0.99	0.19	0.65	0.16	0.97	0.68	0.60
Lifetime Alcohol Dependence	-0.43	0.66	1.50	0.54	0.60	0.32	0.48	0.51	0.92	0.94
<= High School	-0.17	0.81	0.84	0.72	0.07	0.87	-1.40	0.76	2.17	0.30
Symptoms –Pre Injury										
Headache	2.13	0.002**	2.86	0.03*	1.17	0.004**	7.88	0.06	1.59	0.54
Anxiety	2.50	0.006**	5.03	0.01*	1.37	0.01*	16.49	0.001**	5.26	0.05*
Depression	1.06	0.33	2.35	0.23	0.77	0.24	15.86	0.02*	3.33	0.19
Concentration	1.80	0.03*	1.70	0.34	1.51	0.002**	8.08	0.13	4.55	0.05*
Dizziness	0.77	0.55	1.78	0.50	0.78	0.32	2.01	0.78	--	--
Memory	0.22	0.78	1.18	0.75	0.87	0.07	5.91	0.21	3.45	0.10
Vision	0.23	0.86	0.84	0.85	1.11	0.15	2.15	0.78	--	--

Table 16: The Univariate Effect of Independent Variables on Various 12 month Outcomes

	Number of Symptoms		4 or More Symptoms		Natural Log of Severity of Symptoms		Lack of Well Being		Inability to Return to work/school (full or part-time)	
Thinking	0.76	0.59	1.14	0.89	0.69	0.42	4.10	0.60	2.27	0.49
Irritable	1.69	0.02*	2.64	0.04*	1.21	0.004**	3.51	0.42	1.08	0.93
Tired	1.52	0.03*	2.49	0.08	1.14	0.006**	3.49	0.42	1.67	0.55
Light Sensitivity	0.87	0.33	0.93	0.91	0.69	0.20	3.06	0.60	1.52	0.63
Noise Sensitivity	1.88	0.12	2.46	0.26	0.50	0.50	11.02	0.12	1.79	0.62
Physical	2.68	0.002**	4.31	0.07	1.82	<0.001**	7.61	0.15	1.52	0.70
Emotional	2.28	0.001**	4.56	0.002**	1.56	<0.001**	9.11	0.03*	1.59	0.54
Cognitive	1.32	0.06	1.40	0.47	1.44	<0.001**	8.98	0.04*	2.94	0.16
Symptoms –3-10 Days Post-Injury										
Headache	1.37	0.06	3.33	0.03*	0.82	0.06	2.04	0.66	0.72	0.68
Anxiety	1.91	0.005**	3.88	0.006	0.85	0.04*	10.86	0.01*	1.20	0.81
Depression	0.82	0.23	2.13	0.11	0.91	0.03*	6.89	0.10	2.27	0.29
Concentration	1.57	0.03*	2.19	0.13	0.74	0.09	5.56	0.22	3.70	0.23
Dizziness	0.79	0.29	0.78	0.61	0.37	0.41	-3.18	0.50	0.37	0.20
Memory	1.24	0.07	1.14	0.77	1.08	0.008**	10.07	0.014*	9.09	0.05*
Vision	0.99	0.16	1.62	0.31	0.77	0.07	0.36	0.93	1.05	0.95
Thinking	2.11	0.006**	3.04	0.03*	1.06	0.02*	11.80	0.01*	1.89	0.42
Irritable	1.86	0.01*	4.33	0.02*	1.24	0.005**	5.11	0.26	1.22	0.82
Tired	1.23	0.35	3.22	0.30	0.11	0.89	0.23	0.98	--	--
Light Sensitivity	1.49	0.03*	2.33	0.08	1.05	0.013*	2.78	0.52	0.98	0.98
Noise Sensitivity	1.90	0.01*	3.06	0.03*	0.72	0.11	11.36	0.01*	1.49	0.61
Physical	1.33	0.54	--	--	-0.29	0.83	-2.01	0.91	--	--
Emotional	1.63	0.001**	--	--	1.61	0.002**	11.92	0.02*	--	--
Cognitive	1.63	0.06	1.41	0.56	1.36	0.007**	8.03	0.15	--	--